



# ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 69

Alan R. Katritzky

Advances in

# Heterocyclic Chemistry

Volume 69

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Advances in

# HETEROCYCLIC CHEMISTRY

*Edited by*

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**Volume 69**



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## Preface

Volume 69 of *Advances in Heterocyclic Chemistry* consists of six contributions. The opening chapter, by Professor R. M. Moriarty and Dr. O. M. Prakash of the University of Illinois at Chicago, summarizes the use of organohypervalent iodine reagents in the synthesis of organic compounds, a subject of increasing importance and one for which no general review has as yet appeared.

Dr. István Hermecz (Chinoin, Budapest, Hungary) covers the chemistry of pyrido[1,2-*b*][1,2]oxazines, -thiazines, and -pyridazines and their benzo-logs, compound classes that have not previously been reviewed but which in recent years have shown increasing significance with regard to their biological and other properties. This forms the first installment of a set of three chapters: the subsequent installments in later volumes of our series will deal with (i) [1,2-*c*]-fused 1,3-oxazines, 1,2-thiazines, and pyrimidines; (ii) [2,1-*b*]-fused analogs; and (iii) fused 1,4-oxazines and 1,4-thiazines.

Volume 69 also contains the third and final section of the comprehensive overview of acyclonucleosides by Professor El Ashry and Dr. El Kilany of the Chemistry Department of Alexandria University, Egypt. The same authors published Part 1 of the set in Volume 67 and Part 2 in Volume 68. The present Part 3 covers *tri*-, *tetra*-, and *pentaseco*-nucleosides, including many compounds of considerable interest because of their relationship to newer anti-AIDS drugs.

Professor Erich Kleinpeter of the University of Potsdam, Germany, provides the first comprehensive review of the conformational analysis of saturated 6-member oxygen-containing rings, comprising the oxanes, various dioxanes, trioxanes, and tetroxanes. Heteropentalenes with fused imidazoles or 1,2,4-triazole rings is the subject of the chapter by Dr. Lüpfer and Professor Friedrichsen from the University of Kiel, Germany. This chapter is the first comprehensive review of this class, although portions of the subject have been covered in various places before. The compounds are important not only because of their biological properties but also because of potential uses as new materials.

The final chapter in Volume 69 is concerned with the synthesis, stereochemistry, and transformation of cyclopentane-, cyclohexane-, cycloheptane-, and cyclooctane-fused 1,3-oxazines, 1,3-thiazines, and pyrimidines and is authored by Professors Ferenc Fülöp, Gábor Bernáth, and Kalevi Pihlaja from the Universities of Szeged in Hungary and Turku in Finland. This is a field which has shown rapid development over the last dozen years because of the increased availability of spectroscopic and other analytical methods allowing definition of the precise steric chemistry of these compounds.

ALAN R. KATRITZKY

# Synthesis of Heterocyclic Compounds Using Organohypervalent Iodine Reagents

ROBERT M. MORIARTY AND OM PRAKASH\*

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Chicago, Illinois 60607*

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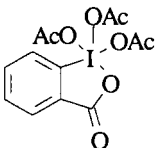
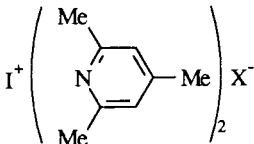
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## I. Introduction

Organohypervalent iodine reagents contain iodine in higher than the I(I) valence state, that is, I(III) and I(V). They have found wide use as oxidants in organic synthesis (66CRV243; 81CSR377; 83MI1, 83YGK251; 84CHEC563, 84S709; 86ACR244, 86YGK660; 87RCR826; 90S431, 90SL365; 92AGE274, 92MI1; 94H409, 94MI1, 94MI2; 95MI1–MI4; 96CRV1123; 97MI1; 97T1179). Many of their reactions lead to heterocyclic products, and these processes are of significant preparative utility. Although some specialized articles have covered this aspect (94H409, 94MI1, 94SL221), a general review has not previously appeared. The present review is a comprehensive coverage of the synthesis of heterocyclic compounds using organohypervalent iodine reagents.

The classification adopted in this chapter is ordered based on the ring size/type of heterocyclic systems synthesized. It is useful to list the names, common abbreviations, and formulas of organohypervalent iodine reagents used in the discussion of results (Table I).

TABLE I  
ORGANOHYPERVALENT IODINE REAGENTS

Formula	Name(s)	Abbreviation
$\text{PhI}(\text{OAc})_2$	Iodobenzene diacetate or (diacetoxyiodo)-benzene	IBD
$\text{PhI}(\text{O}_2\text{CCF}_3)_2$	Iodobenzene bis(trifluoro)acetate or [bis(trifluoroacetoxy)iodo]benzene	IBTA
$\text{PhI}(\text{OH})\text{OTs}$	[(Hydroxy)(tosyloxy)iodo]benzene or Koser's reagent	HTIB
$\text{PhI}(\text{CN})\text{OTf}$	[(Cyano)(trifluoromethanesulfonyl)-iodo]benzene or cyano(phenyl)-iodonium triflate	
$t\text{-BuC}_6\text{H}_4\text{IF}_2$	4- <i>tert</i> -Butyl(difluoroiodo)benzene	
$\text{PhI}(\text{OH})\text{OPO}(\text{OPh})_2$	[Hydroxy((bis(phenoxy)phosphoryl)oxyiodo)benzene	
$(\text{PhIO})_n$	Iodosylbenzene or iodosobenzene	
	1,1,1-Tris-acetoxy-1,2-benziodoxolin-3-(1 <i>H</i> )-one or Dess-Martin reagent	
	Bis( <i>sym</i> -collidine)iodine (I) salts X = $\text{ClO}_4$ X = $\text{BF}_4$	BCIP

## II. Synthesis of Heterocyclic Compounds

### A. GENERAL CONSIDERATIONS

Syntheses of heterocyclic compounds that are dealt with in this review are achieved either by cyclization of open-chain substrates under the action of organohypervalent iodine reagents or by carrying out several sequential transformations of substrate heterocyclic compounds using these reagents to obtain new heterocyclic derivatives. In this section, we cover the first strategy, leaving the second one for Section III. An area that is not covered

in this review is nucleophilic aromatic substitution using heteroaryl iodonium salts (95MI5).

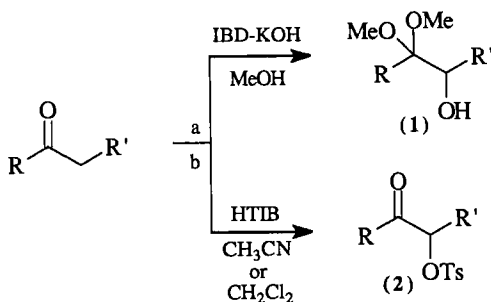
Five types of methods involving fundamental organohypervalent iodine reactions that can be used in heterocyclic synthesis from an open-chain precursor are presented in the following sections.

### 1. *Synthesis via $\alpha$ -Functionalization of Carbonyl Compounds*

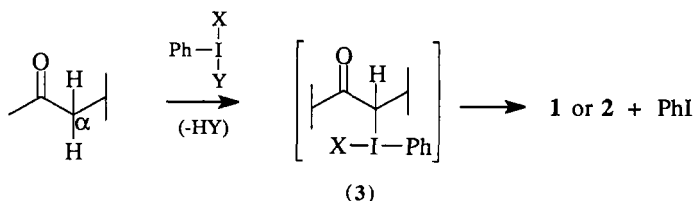
The largest number of examples involves cyclization of easily accessible  $\alpha$ -functionalized open-chain carbonyl compounds. Two important reactions that find general applicability for the  $\alpha$ -functionalization are outlined in Scheme 1. Route (a) shows the formation of  $\alpha$ -hydroxydimethylacetals **1** (81TL1283; 86ACR244), while route (b) results in  $\alpha$ -tosyloxyketone **2** formation (82JOC2487; 90SL365).

The step common to both of these reactions is electrophilic attack of a hypervalent iodine species at the  $\alpha$ -carbon of the carbonyl compounds to yield an  $I^{(III)}$  intermediate **3**. Nucleophilic attack of methoxide ion or tosyloxy ion with the concomitant loss of iodobenzene results in  $\alpha$ -functionalized carbonyl compounds (Scheme 2).

The way in which this process finds application in heterocyclic synthesis is via intramolecular cyclization involving a heteroatom nucleophilic displacement either at the carbon-tosylate center of **2**, or via heteroatom participation in the intramolecular decomposition of intermediate **3**.  $\alpha$ -Tosyloxyketones (**2**) accessible through [(hydroxy)(tosyloxy)iodo]benzene (HTIB)-induced oxidation are of particular interest because of their relationship to the analogous  $\alpha$ -halogenoketones, which are key intermediates for a wide range of heterocycles (83MI2). An illustration of the method embodied in Scheme 2 in which **3** undergoes cyclization via attack by an intramolecular heteronucleophile is shown in Scheme 3.



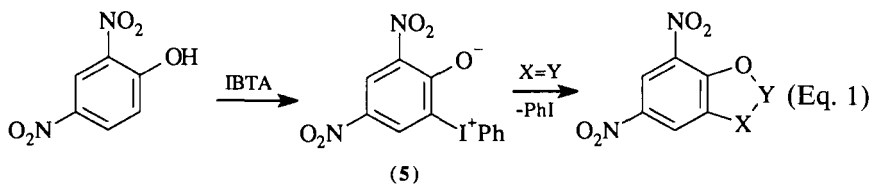
SCHEME 1



SCHEME 2

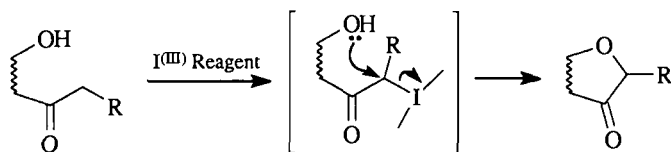
## 2. Synthesis via Iodonium Ylides/Salts

Formation of stable iodonium ylides or salts, a property of certain organoiodine(III) reagents (83MI1; 92MI1; 95MI4), constitutes another series of useful syntheses. Three important types of iodonium ylides having general applicability for these syntheses are prepared from (i)  $\beta$ -dicarbonyl compounds that can yield the 1,3-dipolar keto carbene system (Scheme 4) (57ZOB2737; 83S392; 89JA6443), (ii) phenols containing at least one electron-accepting group in the *para* position and one free *ortho* position (57JCS295; 77TL4113; 79JA5858; 88TL677; 92TL6519) (Eq. 1), and (iii)



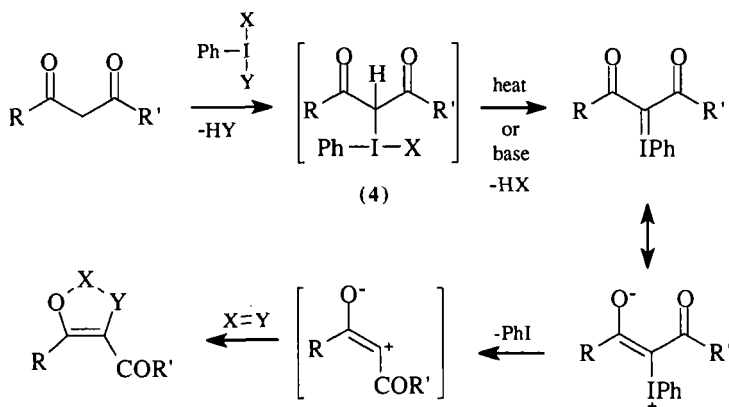
sulfonamides or amines (74JOC340; 75CL361; 87TL877) (Scheme 5). The first step in the ylide generation is the formation of  $I^{(III)}$  intermediate **4** (analogous to **3**, Scheme 2), which subsequently loses an  $\alpha$ -proton under the influence of heat or base to give the stable ylide (Scheme 4).

Besides iodonium ylides, alkynyliodonium salts are also useful in heterocyclic synthesis. These salts are obtained from the reaction of the alkynes with an appropriate organohypervalent iodine reagent (Scheme



SCHEME 3

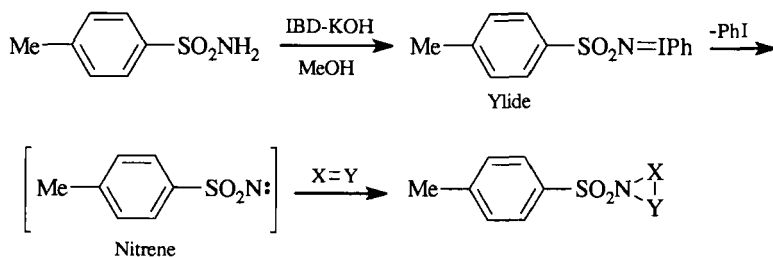


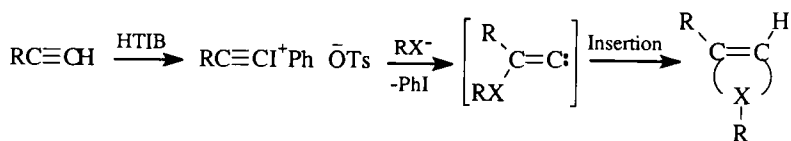


6) (65JOC1930; 79DOK607; 81JOC4324; 84JOC4700, 84JOC4703; 90JOC1513; 92AGE274; 94MI1; 95MI3). These iodonium salts on decomposition generate carbenes, which then provide various heterocycles.

### 3. Synthesis via Phenolic Oxidations

Oxidation of phenols with hypervalent iodine reagents is known to give quinone derivatives initiated via the electrophilic attack of  $I^{(III)}$  reagent at the phenolic group [87JOC3927; 89S126; 93JCS(P1)1891; 96T1303] followed by intramolecular cyclization (Scheme 7). This reaction provides the basis for several syntheses discussed in this review.

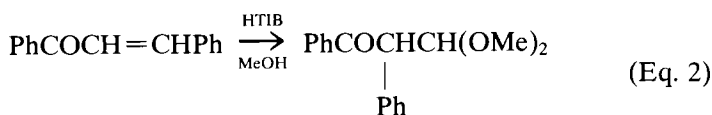




SCHEME 6

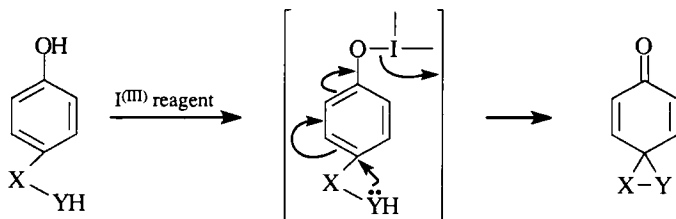
#### 4. *Synthesis via Oxidative Rearrangements*

Oxidative rearrangements resulting in the formation of heterocyclic compounds are relatively less explored, although some of them are quite important. A basic reaction is the conversion of a chalcone to 3,3-dimethoxy-1-phenylpropanone (Eq. 2) (85TL2961). This process may be adapted to heterocyclic synthesis.



#### 5. *Synthesis via Oxygen Transfer or Radical Processes*

In contrast to the *processes 1–4* where organohypervalent iodine compounds behave as the electrophilic species, other approaches deal with reactions where these reagents either act as oxygen transfer agents (nucleophilic or radical) or undergo radical processes.

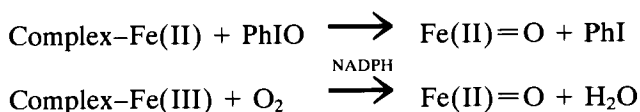


SCHEME 7

## B. THREE-MEMBERED RING HETEROCYCLES

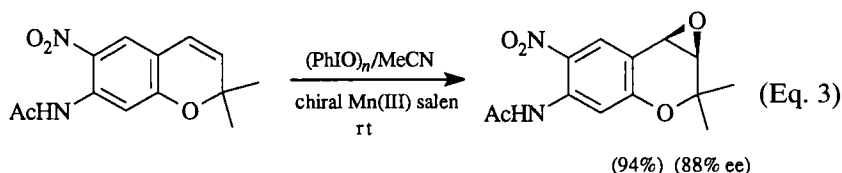
1. *Oxiranes and Oxiranones*

Oxidation of certain acyclic and cyclic olefinic compounds with iodosobenzene under suitable conditions leads to the formation of oxiranes (epoxidation). An approach that is significant both from theoretical and practical point of view involves cytochrome P-450 or synthetic porphyrins or analogs of simpler structure coordinated with metals as catalysts in the oxygen transfer reactions of iodosobenzene [83JA5791; 84JA814; 85CL665, 85TL4699; 86JA2309, 86MI1; 87JCS(CC)803, 87JOC4545, 87TL4553; 89CL1269, 89IC950, 89JA4517, 89JA7443; 89LA171; 90JCS(P2)1917]. The concept underlying these studies is that iodosobenzene acts as a surrogate for molecular dioxygen in combining with Fe(II) or Cu(I) and other metals.

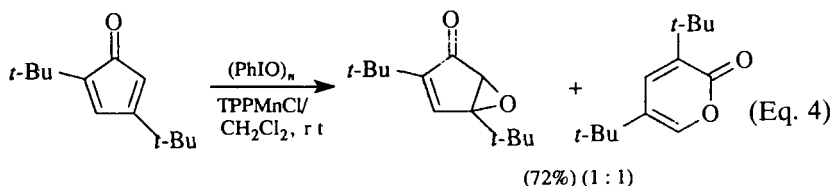


This system of metal and iodosobenzene has resulted in important theoretical insights but so far has not achieved preparative significance for the formation of oxiranes compared with the reaction shown in Eq. (3).

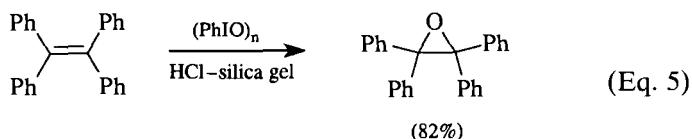
A series of olefins has been converted to the corresponding oxiranes by using iodosobenzene in the presence of catalysts such as [bis(salicylidene)ethylenediamine]manganese(III) complex [chiral Mn(III) salen]. These reactions are generally regioselective and stereoselective, as exemplified by highly enantioselective epoxidation of 2,2-dimethylchromenes using chiral Mn(III) salen as a catalyst (Eq. 3) (92SL407).



Oxidation of dienones with iodosobenzene in the presence of a catalytic amount of tetraphenylporphinatomanganese(III) chloride [TPP(III)C1] affords a mixture of the corresponding oxiranes and 2-pyrones (85CL665) (Eq. 4).

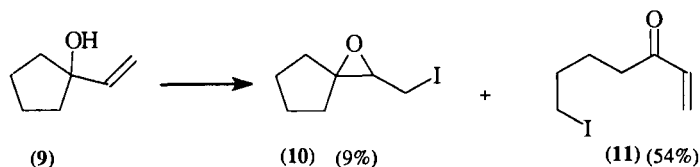


Equation (5) illustrates an example of the recently developed solid-state oxirane synthesis using iodosobenzene (91CL1391; 92CL891).

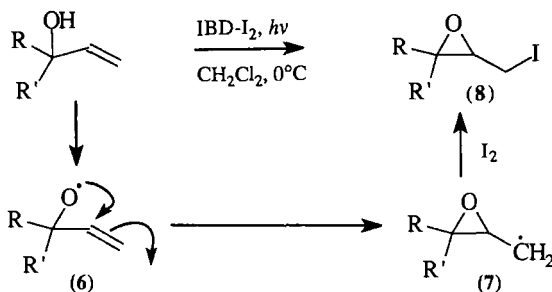


2-Iodomethyloxiranes **8** are the products when aliphatic tertiary alcohols are oxidized with IBD- $I_2$  under photochemical conditions (91TL7493). These conditions presumably generate alkoxy radical **6**, which is then cyclized to generate radical **7** and is finally trapped by the molecular iodine to give the product **8** (Scheme 8). A similar approach is applicable to synthesize reduced furans, medium-sized lactones, etc. [86TL383; 91JCS(P1)3349; 95TL7089].

1-Vinylcyclopentanol (**9**) gives the spirooxirane (**10**) in 9% yield. The major product in this case is an iodoenone **11**, which results from  $\beta$ -scission of the intermediate alkoxy radical.

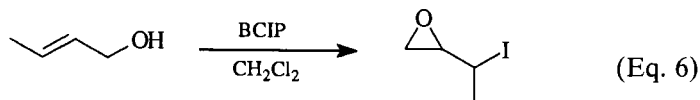


In a related study, Evans *et al.* (88S862) introduced a useful approach for the synthesis of three- to seven-membered ring iodo ethers generally

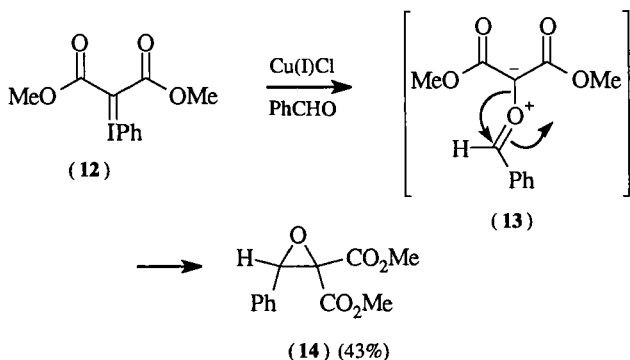


SCHEME 8

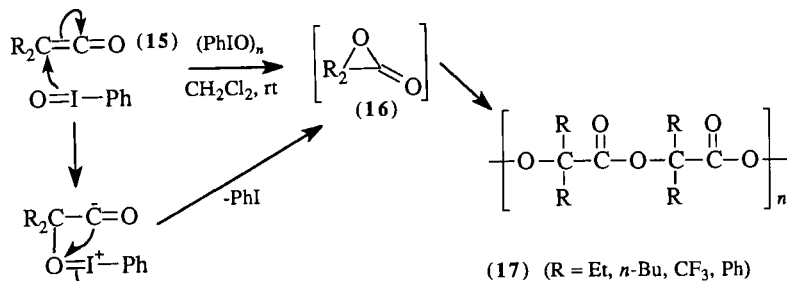
with high regioselectivity. Their approach is especially useful for the synthesis of oxiranes and oxetanes. Thus, unsaturated alcohols have been cyclized to 2-(1-iodoalkyl)oxiranes by using bis(*sym*-collidine)iodine(I) perchlorate (BCIP) (Eq. 6).



Copper(I) catalyzed decomposition of iodonium ylide **12** in the presence of a large excess of benzaldehyde results in the formation of oxirane **14**. The reaction probably occurs via carbonyl ylide **13**, followed by the ring closure [92JCS(P1)2837].

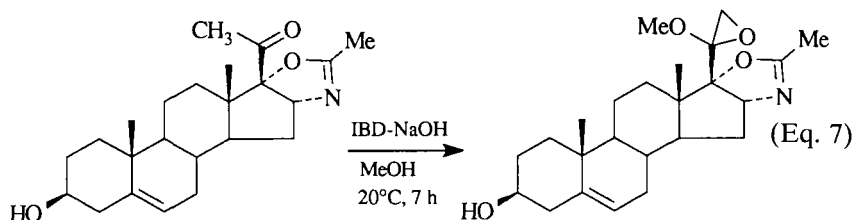


In contrast to the foregoing observations, there are other reactions that generate oxirane derivatives as intermediates that undergo further transformations to a variety of compounds. For example, oxidation of ketenes **15** gives polyesters **17** via the intermediacy of oxiranones **16**. The conversion **15** → **16** probably involves a nucleophilic attack of oxygen end of the iodone–oxygen bond to the ketene double bond, followed by loss of iodo-benzene (81JA686) (Scheme 9).



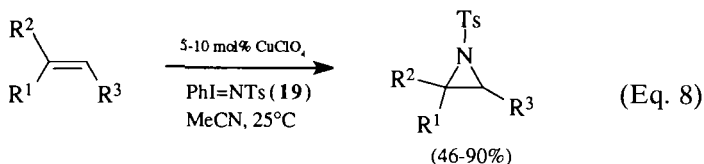
SCHEME 9

Other examples include conversion of ketones to  $\alpha$ -hydroxydimethylacetals **1** (Scheme 1a), which result from a nucleophilic ring opening of the intermediate oxiranes **18** by methoxide ions, as shown in Scheme 10. Interestingly, it is possible to isolate such oxirane derivatives in a few cases such as that shown in Eq. (7) (85S326).

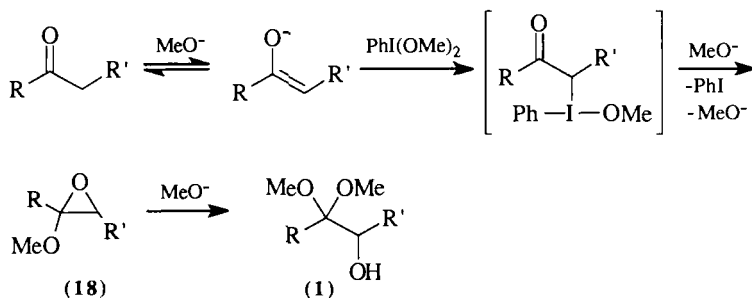


## 2. Aziridines

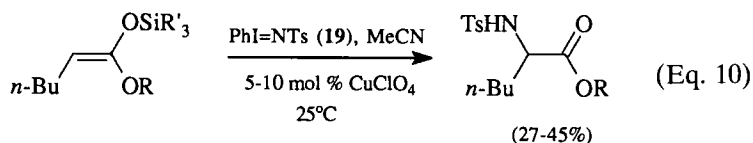
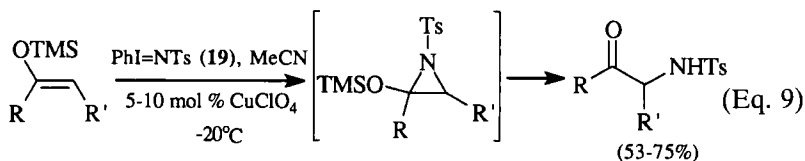
Electron-rich as well as electron-deficient olefins undergo aziridination by decomposition of [*N*-(*p*-tolylsulfonyl)imino]phenyliodinane (**19**) with a catalytic amount of the soluble Cu(I) and Cu(II) triflate and perchlorate salts (Eq. 8) (91JOC6744; 94JA2742). Phenyliodinane **19** acts as nitrene precursor. The Cu(I) catalyzed aziridination when applied to enol silanes



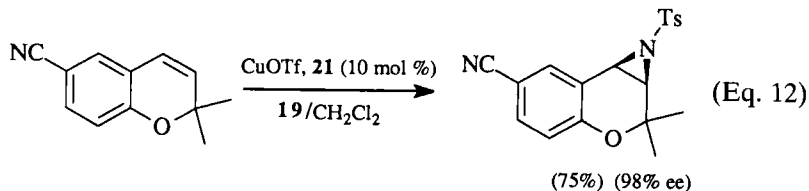
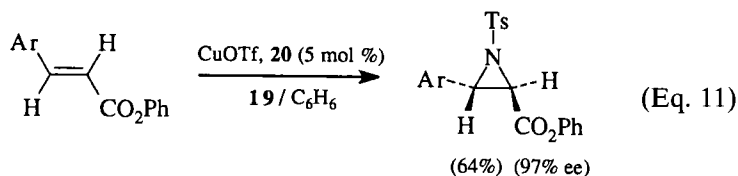
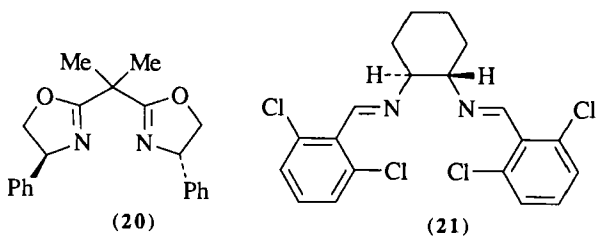
and silyl ketene acetals provides directly  $\alpha$ -aminoketones (Eq. 9) and esters (Eq. 10). The intermediate aziridine derivatives are not isolable in these cases and reaction stereospecificity is found to be both catalyst and substrate dependent.



SCHEME 10

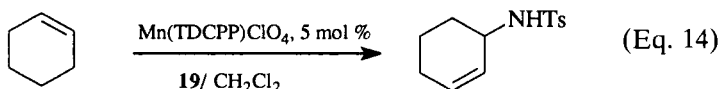
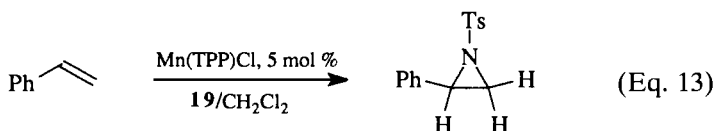


Using chiral copper catalysts formed from chiral ligands **20** and **21**, this approach has been employed to develop enantioselective syntheses of aziridines (91JA726, 91TL7373; 92TL1001; 93JA5326, 93JA5328, 93SL469) (Eqs. 11 and 12).



Apart from Cu(I) and Cu(II) catalysts, Fe(III)- and Mn(III)-derived porphyrin catalysts have also been used in the aziridination of olefins with **19**. However, the latter approach suffers from several drawbacks. For in-

stance, although  $\text{Mn}(\text{TPP})\text{Cl}$ -catalyzed reaction of **19** with styrene affords aziridine derivative in 80% yield (Eq. 13), significantly lower yields are obtained with other olefins. Allylic insertion by the metal nitrenoid is frequently the major side reaction encountered during olefin aziridination (88TL1927) (Eq. 14).

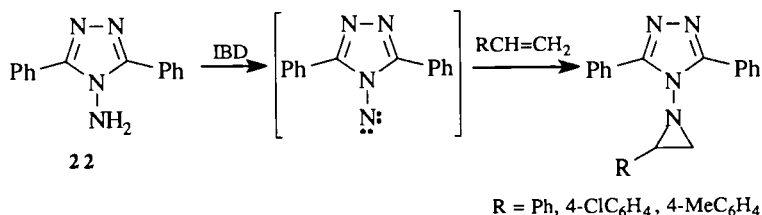


Another aziridine synthesis based on intermediary nitrenes derived from the oxidation of aminotriazole **22** with IBD in the presence of alkenes is outlined in Scheme 11 (74TL2945).

## C. FOUR-MEMBERED RING HETEROCYCLES

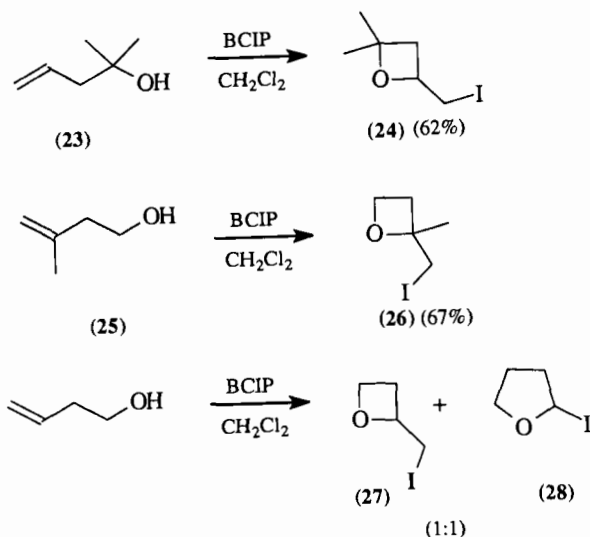
### 1. Oxetanes and Spiro-oxetanes

Iodocyclization of unsaturated alcohols developed by Evans *et al.* (88S862) using BCIP is also applicable for the synthesis of 2-(iodoalkyl)oxetanes. For example, reaction of BCIP with substituted homoallylic alcohols **23** and **25** yields iodomethyloxetanes **24** and **26** in good yields. Iodocyclization of 3-buten-1-ol, however, affords a 1:1 mixture of 2-iodomethyloxetane (**27**) and 2-iodooxolane (**28**).

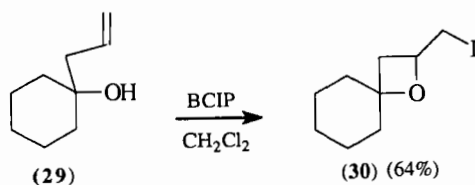


SCHEME 11



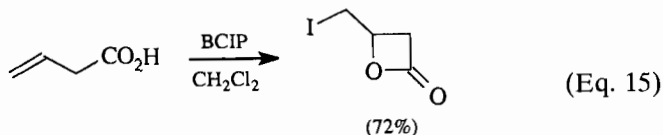


The Evans method gives spiro-oxetane **30** when 2-propenylcyclohexanol (**29**) is employed as the substrate.

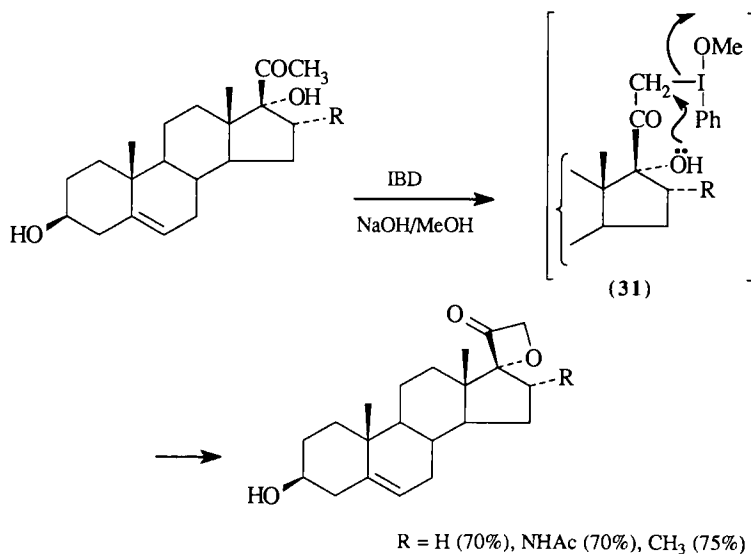


## 2. Oxetan-2-ones and Spiro-oxetan-3-ones

4-(1-Iodoalkyl)oxetan-2-ones are obtained when certain unsaturated carboxylic acids such as 3-butenic acid are treated with BCIP according to the Evans method (Eq. 15).



17- $\beta$ -Acetyl-17-hydroxysteroids on oxidation with IBD lead to the formation of spiro-oxetan-3-ones. The reaction proceeds through an intermediate of the type **31**, which undergoes intramolecular cyclization involving participation of the C<sub>17</sub>-OH group (85S1129) (Scheme 12).



SCHEME 12

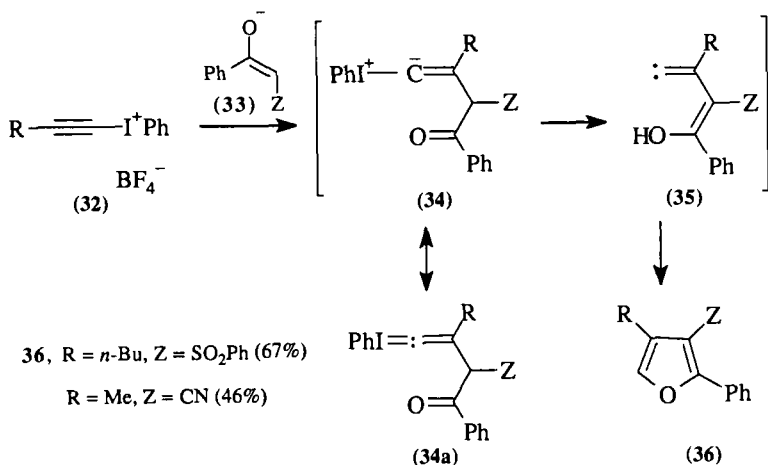
## D. FIVE-MEMBERED RING HETEROCYCLES

### 1. *Furans, Benzofurans, and Related Compounds*

A great deal of work has been reported on the synthesis of furans, benzofurans, and related compounds. For the sake of clarity, the subject matter covered in this section has been divided into four parts that are based on different synthetic approaches as presented in Section II.A.

a. *Using Iodonium Ylides/Salts.* Alkynyliodonium salts such as **32** lead to the synthesis of polysubstituted furans and benzofurans via the tandem Michael–carbene insertion (MCI) reaction. Thus, treatment of  $\beta$ -ketosulfone (**33**, Z = SO<sub>2</sub>Ph) and cyanoketone (**33**, Z = CN) in the presence of *t*-BuONa or *t*-BuOK with alkynyliodonium tetrafluoroborates **32** (65JOC1930; 79DOK607; 81JOC4324; 84JOC4700; 85TL4501) affords the corresponding furans **36** (86JA8281).

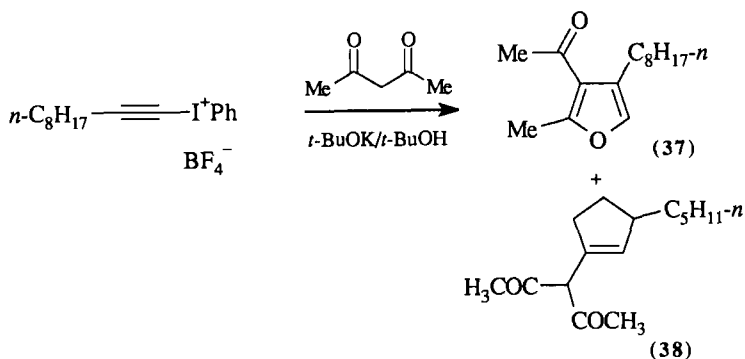
Michael-type addition of an enolate anion to an alkynyliodonium salt probably produces the unstable iodonium ylide **34**  $\leftrightarrow$  **34a**. Loss of PhI from **34** may produce the highly reactive alkylidene carbene **35** (or carbenoid). Intramolecular 1,5-insertion of **35** (enolized) into the enolic O–H bond yields the furans **36** (Scheme 13).



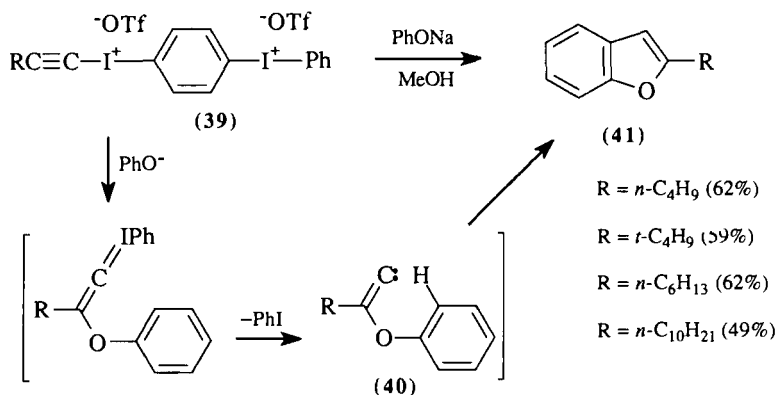
SCHEME 13

Exclusive formation of furans clearly indicates that the intramolecular 1,5-insertion into the C—H bonds of methylene groups cannot compete with that into OH bonds of enols. However, the stereochemistry of enolized carbene intermediates plays an important role in this reaction as acetylacetone affords a mixture of furan **37** and cyclopentene **38** in a 64:36 ratio in 61% yield (Scheme 14).

Alkylidenecarbenes **40** generated by the reaction of alkynyl (*p*-phenylene)bis-iodonium ditriflates **39** with phenoxide anion undergo selective intramolecular aromatic C—H insertion, thereby providing 2-substituted benzofurans **41** (93TL4055) (Scheme 15).

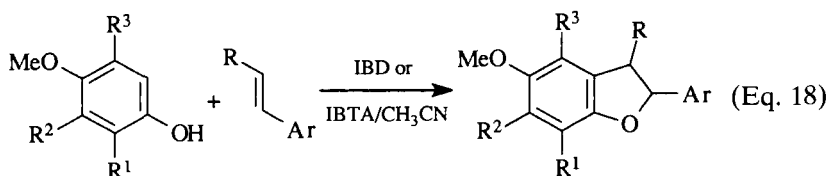
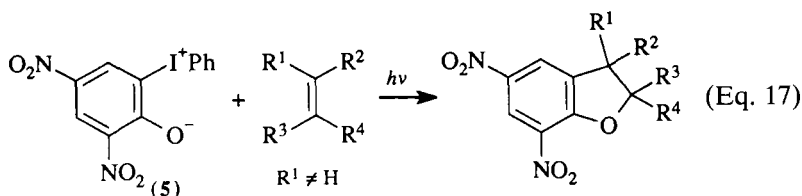
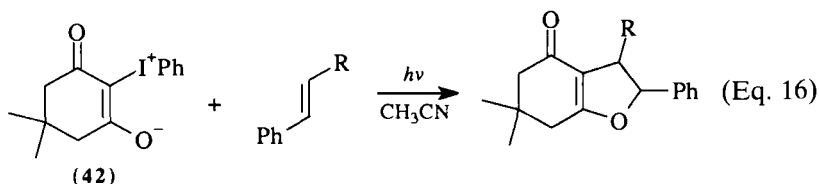


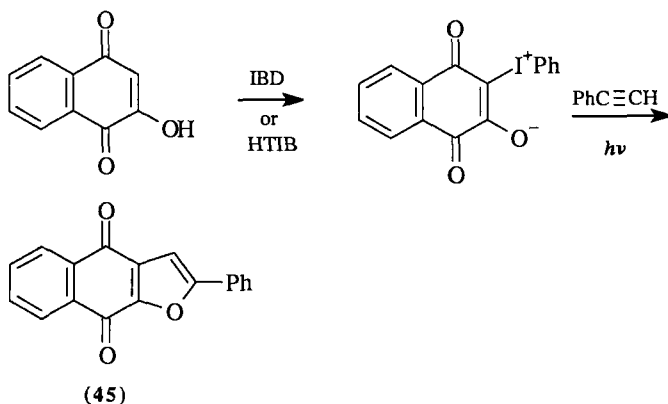
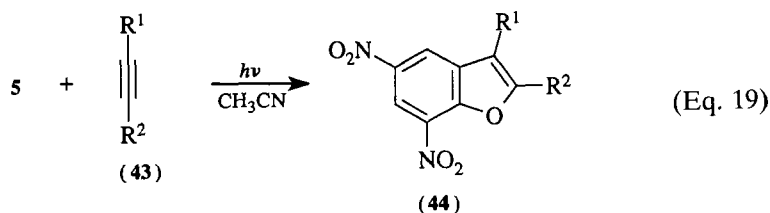
SCHEME 14



SCHEME 15

Other examples of the iodonium ylide-based syntheses of furan derivatives involve cycloaddition reactions with alkenes or alkynes. Although the majority of these syntheses involve stable iodonium ylides (86JOC3453; 94T11541) (e.g., Eqs. 16 and 17), in some cases the ylides are unstable and are generated *in situ* (92JOC2135) (e.g., Eq. 18). In the case of alkenes, dihydrofuran derivatives are obtained (Eqs. 16–18). This synthetic route is especially useful for the synthesis of dihydrobenzofuran derivatives that are related to the *neolignan* family of natural products (Eq. 18).

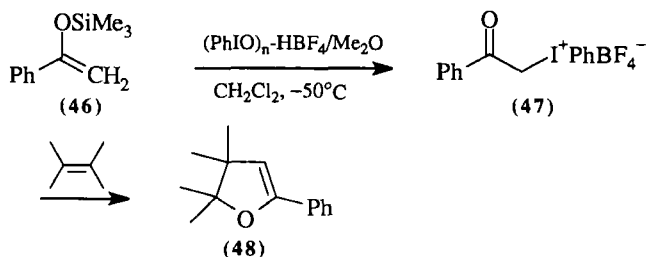




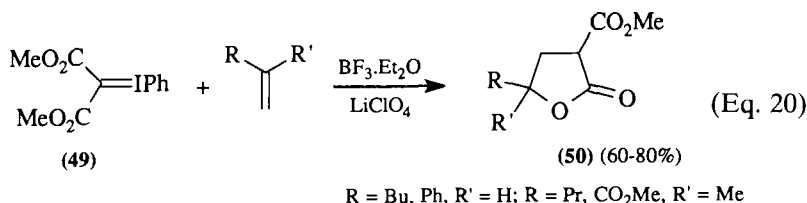
SCHEME 16

When these cycloaddition reactions are carried out with alkynes, furan derivatives are formed. Iodonium ylide **5**, for instance, on photochemical reaction with alkynes **43**, gives benzofurans **44** (86JOC3453) (Eq. 19). In a similar way, the iodonium ylide derived from 2-hydroxy-1,4-naphthoquinone undergoes a cycloaddition reaction with phenylacetylene to yield benzofuran **45** (Scheme 16) (89LA167).

Another important variant of the preceding approach is the cycloaddition reaction between monocarbonyl iodonium salt **47** and an alkene to give dihydrofuran **48** (88TL3703; 89JOC2605). The iodonium salt **47** is generated by the oxidation of acetophenone silyl enol ether (**46**) with iodosobenzene in the presence of fluoboric acid.



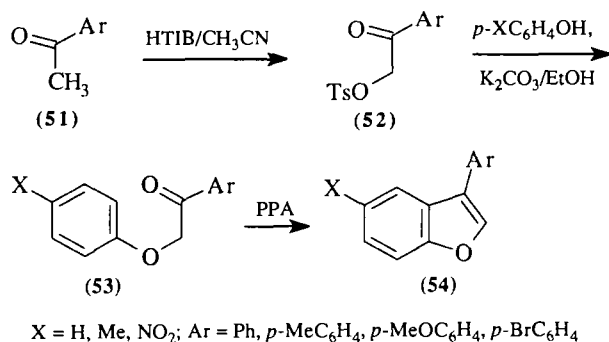
Lewis acid-catalyzed decomposition of iodonium ylide **49** in the presence of alkenes results in the formation of  $\gamma$ -lactones **50** (87IZV2873) (Eq. 20).



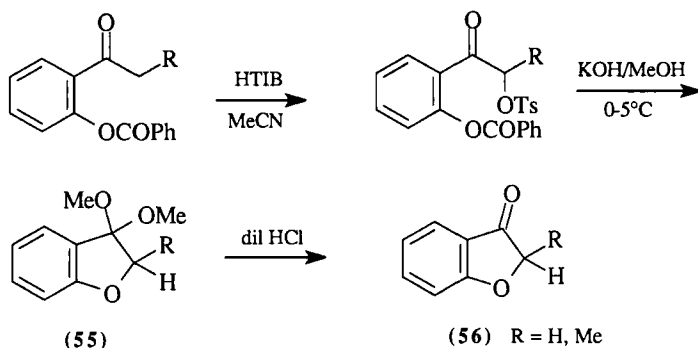
b. *Via  $\alpha$ -Functionalized Ketones.*  $\alpha$ -Tosyloxyketones (**2**), accessible through the route shown in Scheme 1b, can be employed as precursors for 3-substituted benzofurans. Thus,  $\alpha$ -aryloxyacetophenones (**53**), which are obtained by the reaction of  $\alpha$ -tosyloxyacetophenones (**52**) with phenols, undergo cyclization to benzofurans **54** by using standard conditions (95JIC129) (Scheme 17).

2-( $\alpha$ -Tosyloxy)acylphenyl benzoates, obtained from the oxidation of respective 2-acylphenyl benzoates with HTIB, are cyclized to coumaran-3-one dimethylacetals **55** by using KOH in methanol. Acid hydrolysis of **55** affords the corresponding coumaran-3-ones **56** (96UP1) (Scheme 18). Other  $\alpha$ -tosyloxyketones on similar treatment with KOH/MeOH normally give corresponding  $\alpha$ -hydroxydimethylacetals of the type **1**.

Upon oxidation with IBD, a series of *o*-hydroxyacetophenones and related compounds **57** give the corresponding 2-methoxycoumaran-3-ones **59** [84JCS(CC)1342] (Scheme 19). These reactions probably occur via intramolecular participation of the *ortho* hydroxy group, which attacks the  $\alpha$ -carbon of the intermediate **58** to yield the intermediate product **58a**. A similar reaction occurs when  $\beta$ -diketones **60** are oxidized with IBD-KOH/MeOH,



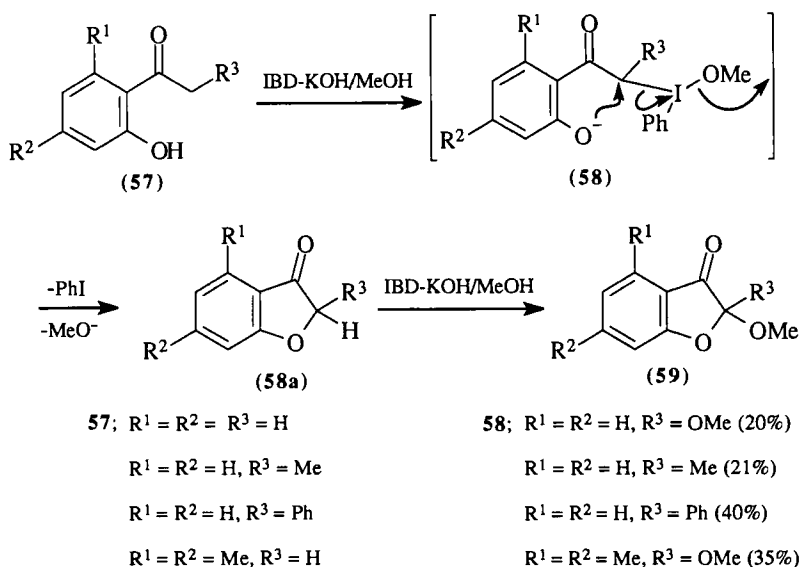
SCHEME 17



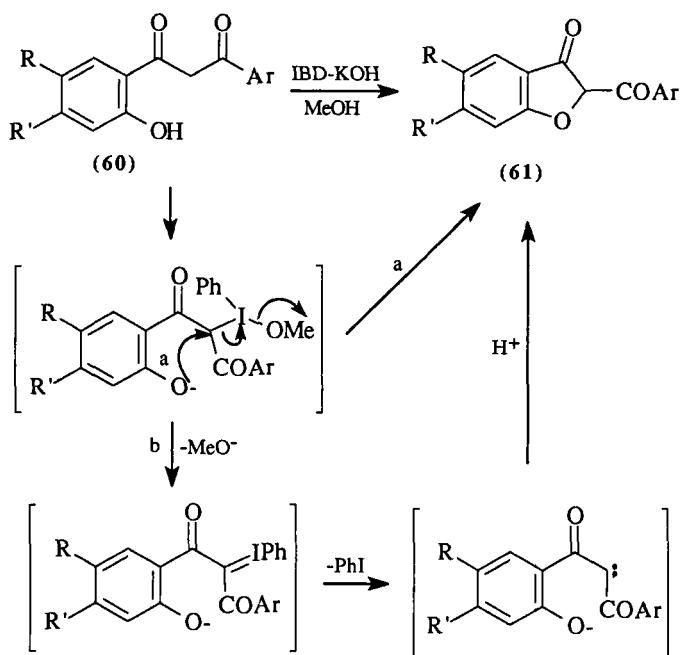
SCHEME 18

but the products are 2-monoaroylcoumaran-3-ones **61** (90SC1409; 92SC2555) (Scheme 20). Although this transformation is believed to occur via route "a," the possibility of generation of carbene from the decomposition of initially formed iodonium ylides (route "b") cannot be ruled out (Scheme 20).

2-Aroylcoumaran-3-ones (**61**) can also be synthesized from the Baker Venkatraman rearrangement of 2-[(tosyloxy)acetyl]phenyl benzoates with potassium hydroxide (92OPP469, 92S629).



SCHEME 19



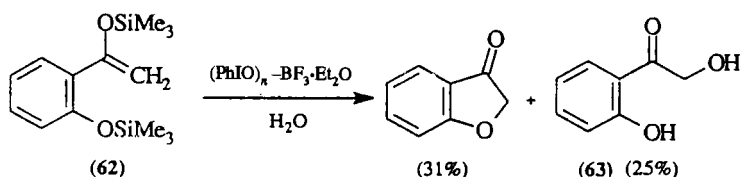
<b>61,</b>	R	R'	Ar	Yield (%)
	H	H	Ph	75
	H	Cl	Ph	--
	Me	Cl	Ph	--
	OMe	H	Ph	--
	H	COMe	Ph	82
	H	COMe	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	80
	H	COMe	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	86
	H	COEt	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	82

SCHEME 20

Coumaran-3-one without substitution at the 2-position can be synthesized by oxidation of silyl enol ether **62** with iodosobenzene under Lewis acid conditions.  $\alpha$ -Hydroxyketone **63** is formed as a side product (86SC1239).

Oxidation of silyl enol ethers leading to carbon-carbon bond formation [85JCS(CC)420; 87JCS(P1)559] finds an interesting application in the synthesis of furans. For example, 1,4-di(3-thienyl)-1,4-butanedione (**65**), which



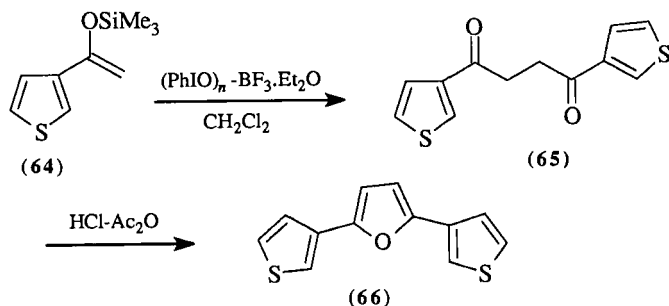


is prepared by the hypervalent iodine oxidation of silyl enol ether **64**, can be converted into 2,5-di(3-thienyl)furan (**66**) (85SC789) (Scheme 21).

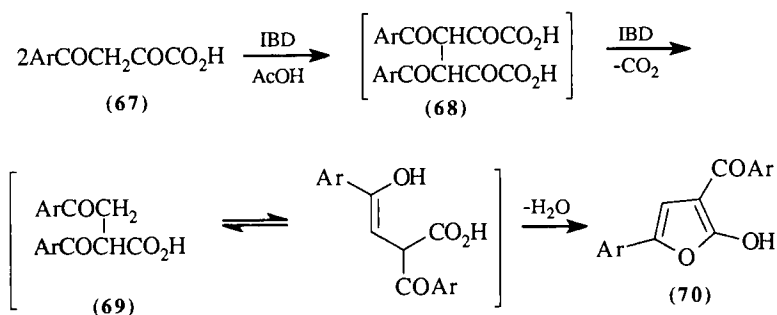
4-Aryl-2,4-dioxobutanoic acids (**67**) upon treatment with IBD afford the corresponding furans **70**. The first step of the reaction is the formation of coupling products **68**, which then expel  $\text{CO}_2$  to give diketo acids **69**. The loss of water from the tautomer of **69** gives cyclized products, enolic lactones **70** (72MI1) (Scheme 22).

c. *Via Phenolic Oxidations.* Hypervalent iodine oxidation of phenols, in conjunction with the thallium(III) oxidative approach, offers a useful synthesis of 4,5-dialkoxyaurones **74** when appropriate chalcones are employed as substrates. Thus, oxidation of *o*-hydroxychalcone **71** with IBTA in methanol leads to the adduct **73a**, formed possibly via the sequence of two Michael additions. Recrystallization of **73a** from ethanol affords the related product **73b**, which presumably is formed by elimination of methanol from **73a** to give **72**, followed by Michael addition of ethanol. The Michael adducts **73a** and **73b** on oxidation with thallium(III) nitrate in methanol provide dialkoxyaurones **74a** and **74b** in 77% and 87% yields, respectively (94TL6441; 95JOC6499) (Scheme 23).

Spirolactones **76** are obtained by intramolecular oxidative cyclization of the appropriate *p*-substituted phenols **75** with  $\text{I}^{(\text{III})}$  reagents (87JOC3927; 92SL201, 92TL6491) (Scheme 24). Using this approach, McKillop *et al.* [92SL201; 96JCS(P1)1385] and Wipf *et al.* (93JOC7195) have accomplished

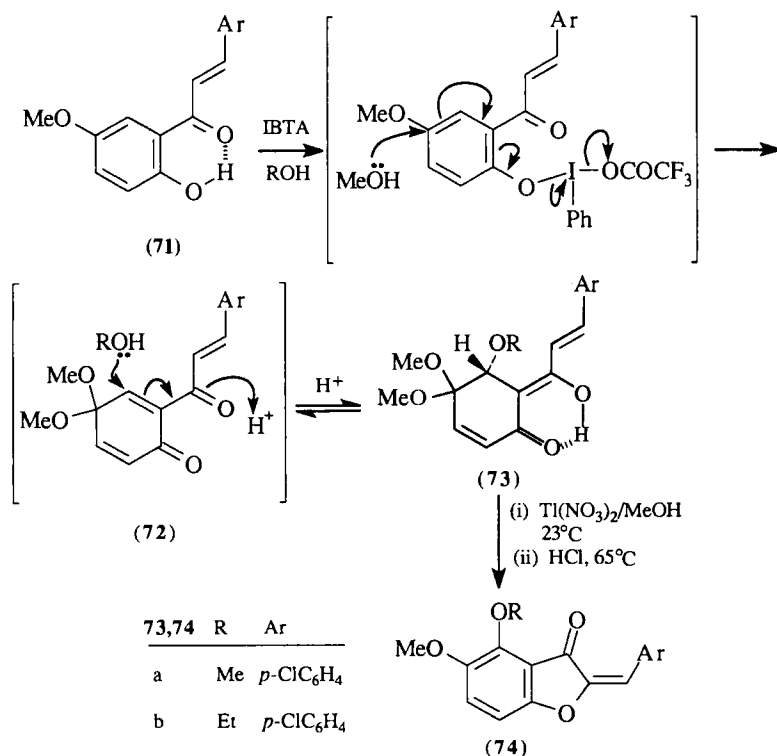


SCHEME 21

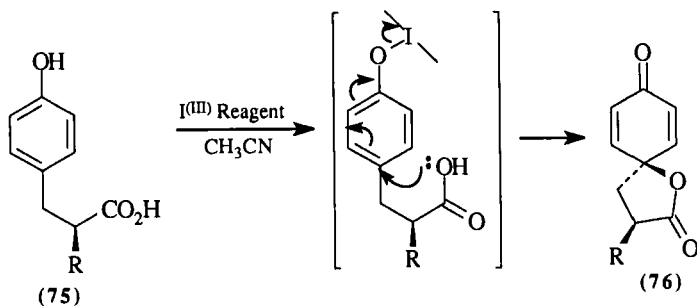


SCHEME 22

the total synthesis of aranorosin (**77**), a natural product isolated from a fungal strain, *Pseudoarachniotus roseus*, which is associated with antibiotic, antifungal, and antitumor activity.

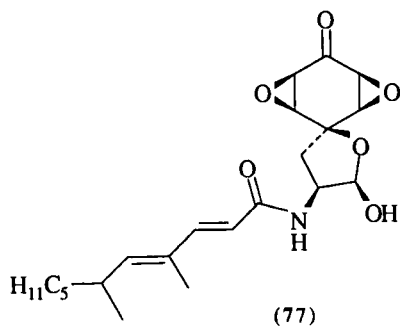


SCHEME 23

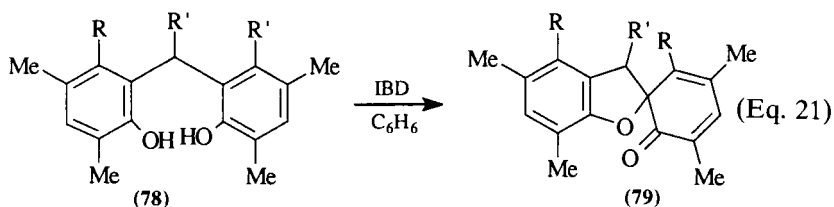


76,	R	I(III) Reagent	Yield (%)
	H	PhI(OCOCH <sub>3</sub> ) <sub>2</sub>	27
	H	PhI(OCOCF <sub>3</sub> ) <sub>2</sub>	83/86
	H	4-MeC <sub>6</sub> H <sub>4</sub> I(OCOCF <sub>3</sub> ) <sub>2</sub>	69
	H	4-ClC <sub>6</sub> H <sub>4</sub> I(OCOCF <sub>3</sub> ) <sub>2</sub>	52
	H	4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> I(OCOCF <sub>3</sub> ) <sub>2</sub>	65
	H	1,4-[I(OCOCF <sub>3</sub> ) <sub>2</sub> ] <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	67
	H	PhI(OH)OTs	53
	NHCOPh	PhI(OCOCF <sub>3</sub> ) <sub>2</sub>	-
	NHAc	PhI(OCOCF <sub>3</sub> ) <sub>2</sub>	28
	NHCO <sub>2</sub> Bn	PhI(OCOCF <sub>3</sub> ) <sub>2</sub>	38
	NHBOC	PhI(OCOCF <sub>3</sub> ) <sub>2</sub>	38

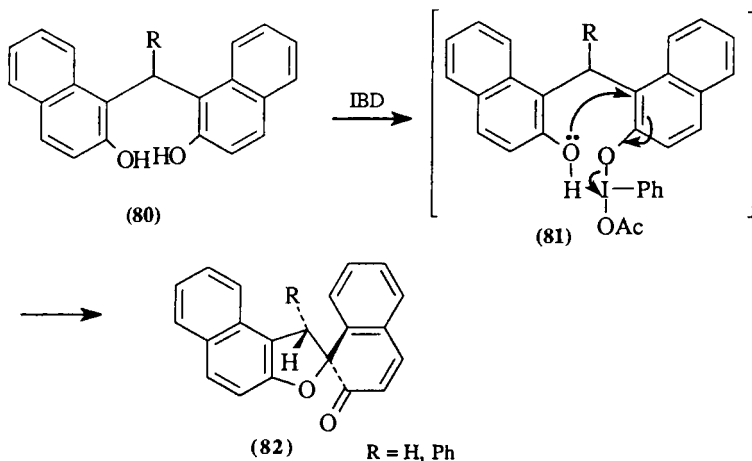
SCHEME 24



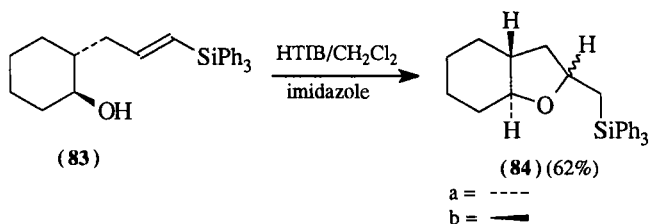
Oxidation of several 1,1-bisphenols **78** with IBD gives spirobenzofuran derivatives of general formula **79** (Eq. 21). This approach, when applied to benzylidene 1,1'-bisanthols **80**, leads to a stereospecific cyclization, thereby forming the less hindered naphtho[2,1-*b*]furan-2(1*H*)-spiro-1'-(2*H*)-naphthalene-2'-ones (**82**) [80JCS(P1)1978, 80JCS(P1)1986]. The conversion **80** to **82** probably occurs through intermediate **81** (Scheme 25).



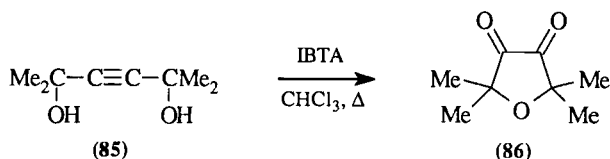
d. *Miscellaneous Methods.* Among the other  $\text{I}^{(\text{III})}$ -mediated methods available for the synthesis of furan derivatives, the most important examples are intramolecular cyclization of several unsaturated alcohols and carboxylic acids. For example, reduced benzofuran derivative **84** is obtained by a HTIB induced stereoselective oxidative cyclization of triphenylsilyl substituted alkenol **83** [90JCS(P1)1481].



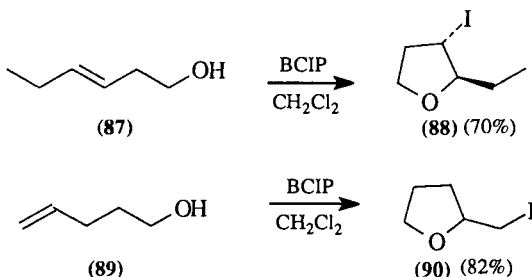
SCHEME 25



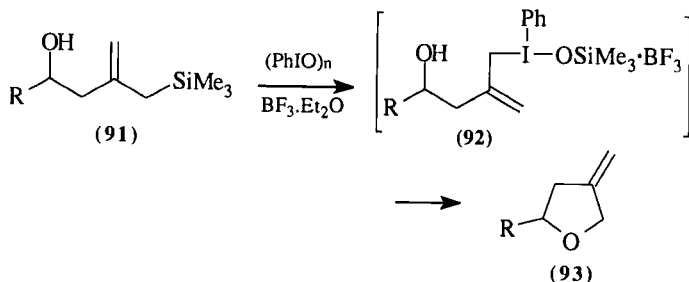
Acetylenic bis-alcohols such as **85** on treatment with IBTA are converted to 3,4-dioxotetrahydrofurans **86** (88ZOR2460).

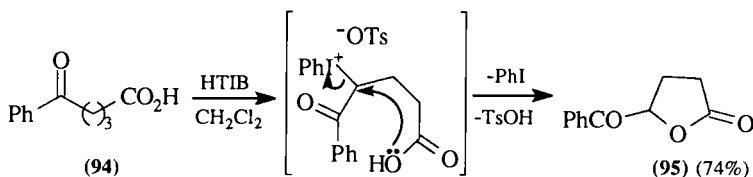


The method developed by Evans *et al.* (88S862) is useful for the synthesis of *trans*-2-ethyl-3-iodotetrahydrofuran (**88**) and 2-iodomethyltetrahydrofuran (**90**) from the alcohols **87** and **89**, respectively.



Reduced furans **93** with  $\beta$ -methylene groups are obtained by an intramolecular reaction of unsaturated alcohols **91** with  $\text{PhI}^+\text{OBF}_3^-$  (generated *in situ* from iodosobenzene and boron trifluoride etherate). This cyclization may proceed via intermediate **92** (85CPB989).



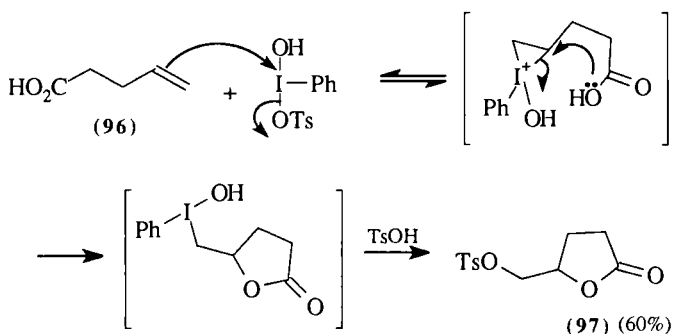
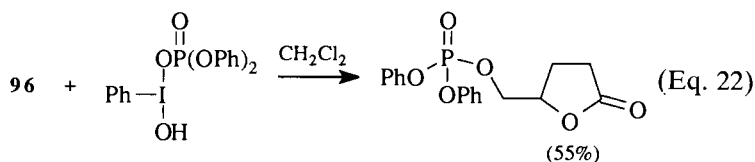


SCHEME 26

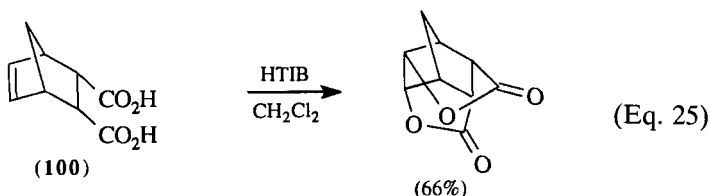
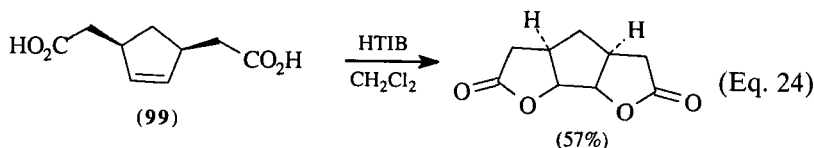
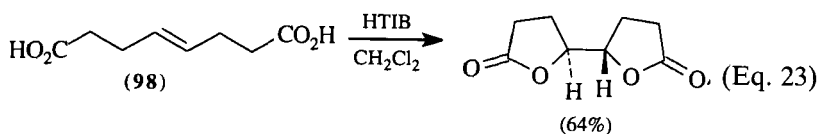
HTIB is found to be a suitable reagent for converting 5-oxocarboxylic acids such as **94** into oxolactones **95**. The reaction occurs via intramolecular participation of the carboxylic group as shown in Scheme 26 (90TL201).

Another HTIB-mediated method resulting in lactone **97** is carried out from 4-pentenoic acid (**96**). The reaction probably involves the capture of one end of the carbon-carbon double bond with tosylate ion and the other with the carboxyl function of the substrate (86TL4557) (Scheme 27). In a similar way, **96** reacts with [hydroxy(bisphenoxyphosphoryloxy)iodo]benzene to yield 5-(bisphenoxyphosphoryl)oxy-4-pentanolactone (88JA2987) (Eq. 22).

The oxidation of alkenedioic acids **98–100** with HTIB leads to the stereospecific production of respective bislactones (86TL5437) (Eqs. 23–25).



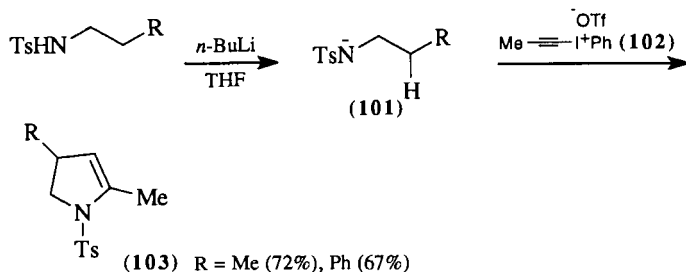
SCHEME 27



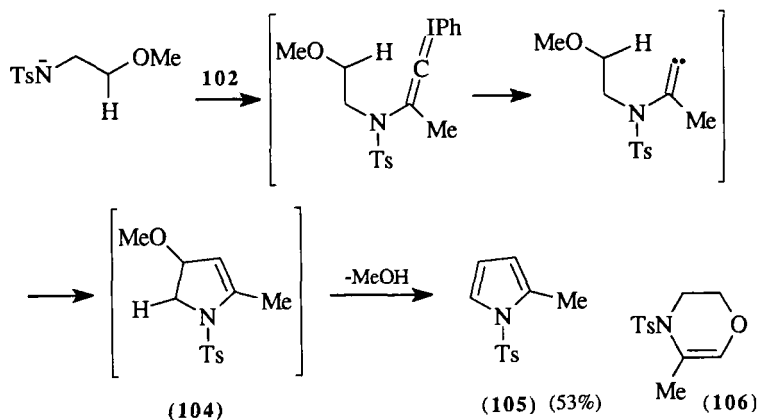
## 2. Pyrroles, Indoles, and Related Compounds

The unique reactivity pattern of alkynyl iodonium salts discussed in Sections II,A,2 and II,D,1a can also serve as two-carbon conjunctive reagents in the synthesis of pyrroles, dihydropyrroles, and indoles. Feldman *et al.* found that combination of alkyl or aralkyl tosylamide anions **101** with phenyl(propynyl)iodonium triflate (**102**) furnishes the corresponding dihydropyrroles **103** (95JOC7722) (Scheme 28).

$\beta$ -Methoxyethyltosylamide also participates in the [3 + 2] addition reaction with **102**, although it does not give any of the expected dihydropyrrole derivative **104**. Instead, the major product was found to be pyrrole **105**, which presumably results through ready elimination of methanol from the putative intermediate **104**. Thus, this addition holds promise for the synthesis of 2-substituted tosylpyrroles (Scheme 29). In addition to **105**, a minor product **106** (12%) is also formed in this reaction.

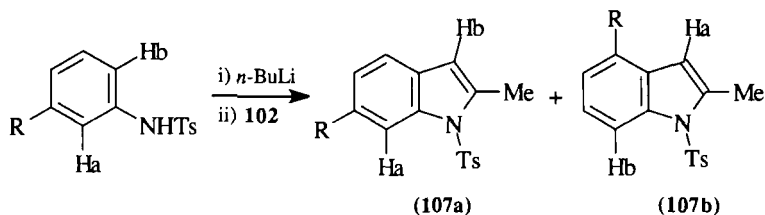


SCHEME 28



SCHEME 29

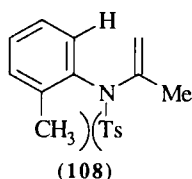
This [3 + 2] addition approach has been extended successfully to indole derivatives. The ready availability of the precursor tosylanilides provides a novel and useful complement to the current approach (94MI3). However, *meta*-substituted tosylanilide yields a mixture of two regioisomeric indoles **107a** and **107b** in different ratios depending on the nature of substituents (Scheme 30). Furthermore, the reaction of *o*-methyltosylamide with **102** does not produce any detectable amount of the desired indole, plausibly due to the repulsive peri-type steric interactions as indicated in **108**, which would be unavoidable as the carbene approaches the CH bond.



R	Yield (%)	107a : 107b
H	66	----
Me	59	1 : 1
OMe	61	1.4 : 1
CO <sub>2</sub> Me	51	1.2 : 1
CO <sub>2</sub> <i>t</i> -Bu	46	1.3 : 1

SCHEME 30



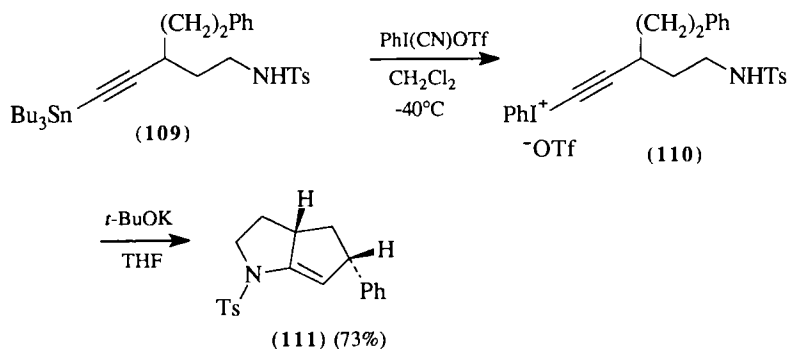


The intramolecular variant of this methodology provides bicyclic nitrogen-containing skeletons such as **111** (95JA7544). The reactive alkynyl-iodonium electrophile **110** can be generated from alkynylstannate precursor **109** as per Stang's procedure (91JA5870) (Scheme 31). This methodology can be employed to form polycyclic alkaloids.

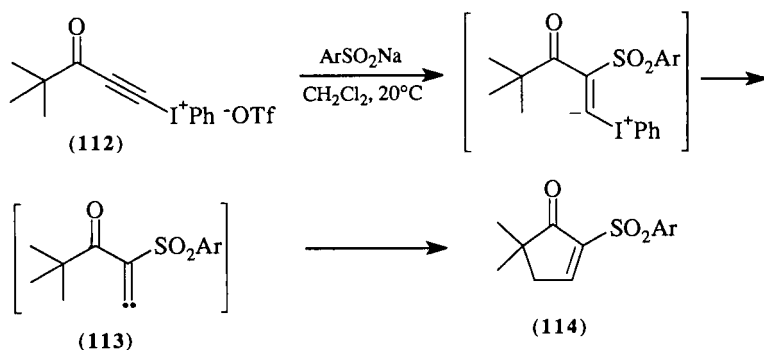
Stang *et al.* (94JA93) have developed another alkynyliodonium salt mediated approach for the synthesis of  $\gamma$ -lactams including bicyclic systems containing the pyrrole moiety. This method is based on the formation of 2-cyclopentenones **114** via intramolecular 1,5-carbon-hydrogen insertion reactions of  $[\beta-(p\text{-toluenesulfonyl})\text{alkylidene}]\text{carbenes}$  **113** derived from Michael addition of sodium *p*-toluenesulfinate to  $\beta$ -ketoethynyl(phenyl) iodonium triflates **112** (Scheme 32). Replacing **112** by  $\beta$ -amidoethynyl (phenyl)iodonium triflates **115–119** provides various  $\gamma$ -lactams as outlined in Eqs. (26)–(30).

Reduced indole derivatives can be synthesized by using the phenolic oxidation approach. Thus, *N*-alkyl-*N*-benzoyltyramines **120**, on treatment with IBTA in trifluoroethanol (TFE), followed by aqueous workup, afford the hexahydroindol-6-ones **122**. The formation of **122** is rationalized by intramolecular Michael-type addition of amino group to the double bond of the intermediate dienone **121** (91JOC435) (Scheme 33).

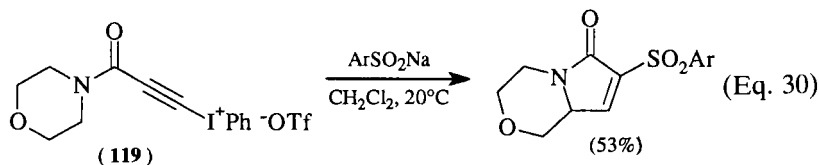
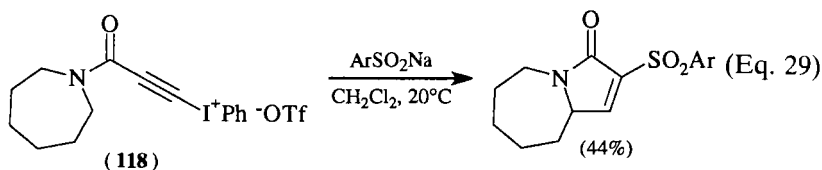
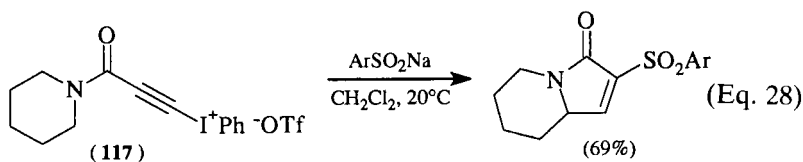
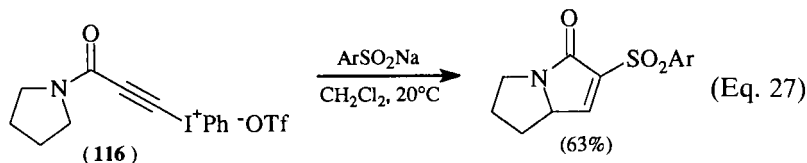
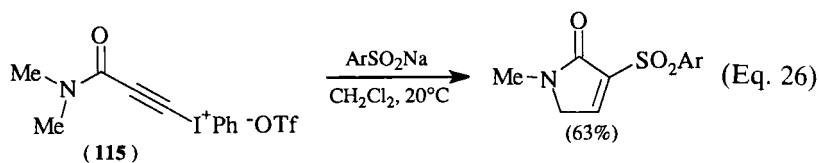
Such an approach has been used to prepare the core hydroindole ring system **123** of *Stema* alkaloids. The actual method involves the oxidation

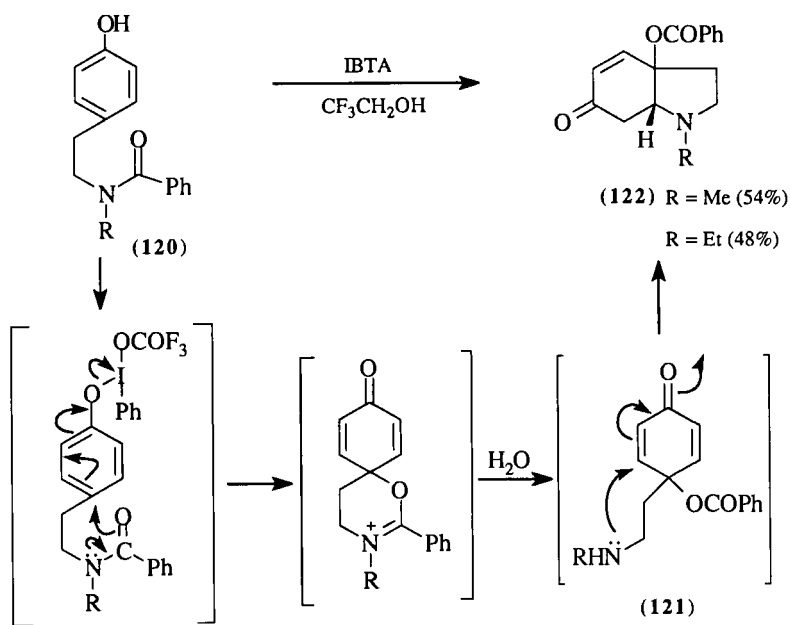


SCHEME 31

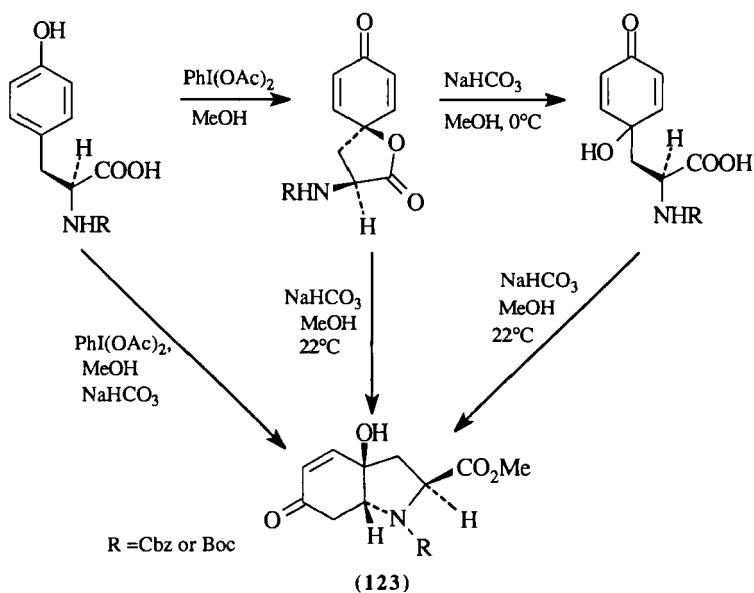


SCHEME 32





SCHEME 33



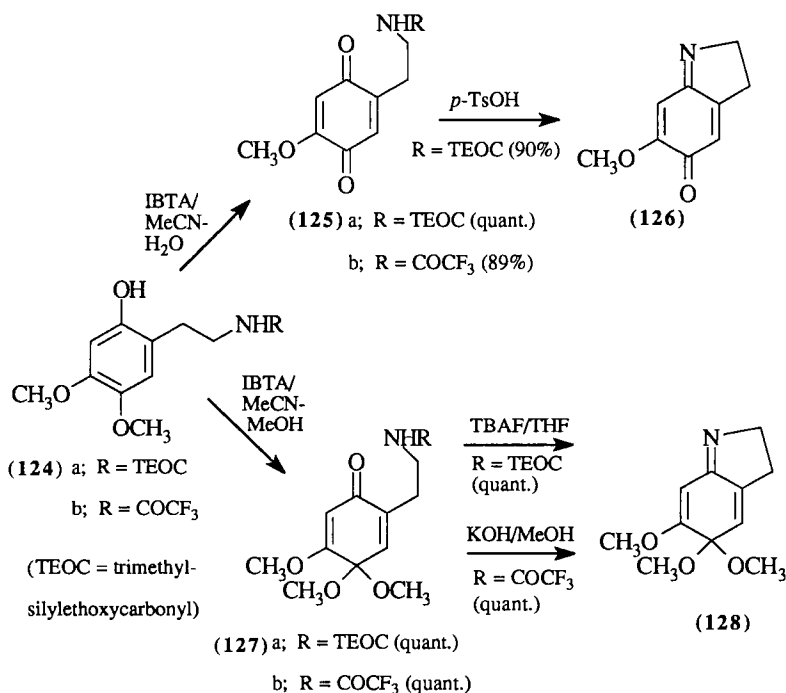
SCHEME 34

of *N*-protected tyrosine with IBD/MeOH in the presence of sodium bicarbonate and the reaction can proceed via three different routes as shown in Scheme 34. This study illustrates an example of exceptional diastereotopic group-selective intramolecular conjugate addition (92TL5477).

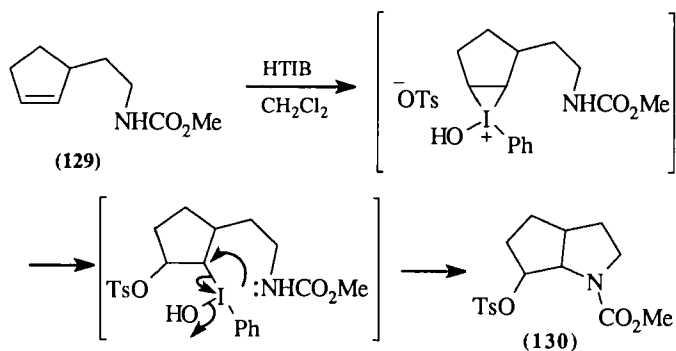
A general and efficient synthesis of 5-oxygenated indoles **126** and **128** has been reported by Kita *et al.* (92H503). The method involves intramolecular imine formation from *p*-benzoquinones **125** and *p*-benzoquinone monoacetals **127** bearing the 2-aminoethyl side chain. Compounds **125** and **127** are prepared by the oxidation of **124** with IBTA in acetonitrile in the presence of water and methanol, respectively (Scheme 35).

Reduced pyrrole derivative **130** is available from the oxidation of carbamate **129**. The reaction proceeds via intramolecular participation of the nitrogen atom of the carbamate function as shown in Scheme 36 (94TH1).

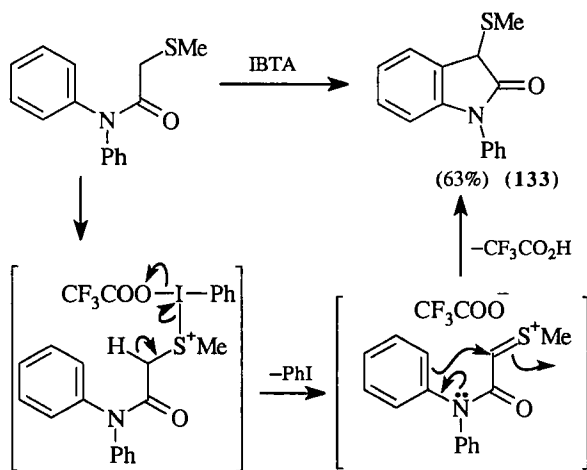
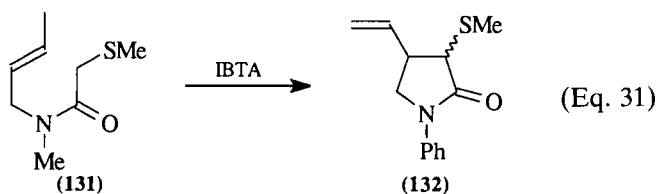
$\alpha$ -Methylthio amide **131** undergoes a Pummerer-type rearrangement with IBTA leading to the formation of 3-methylthiopyrrolidinone **132** (Eq. 31). *N,N*-Diphenyl-2-methylthioethanamide on similar rearrangement gives indol-2(3H)one **133** (86CPB1061; 94H1519) (Scheme 37).



SCHEME 35



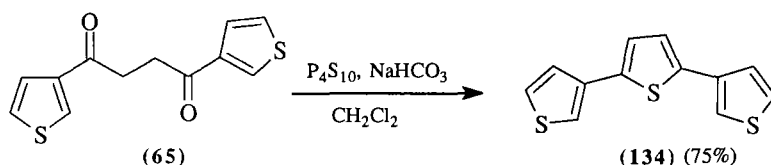
SCHEME 36



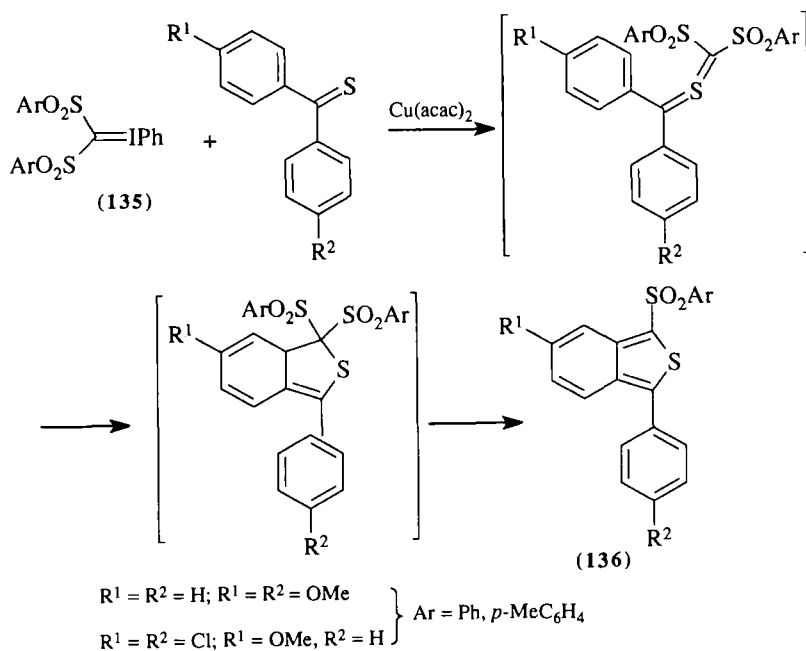
SCHEME 37

### 3. Thiophenes and Benzothiophenes

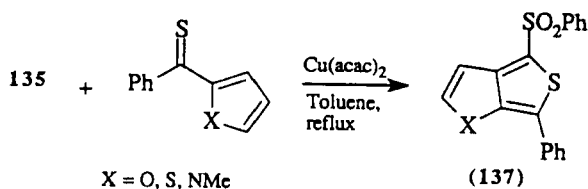
A limited number of hypervalent iodine-mediated synthesis of thiophenes and benzothiophenes have been reported. An indirect approach for the synthesis of thiophenes involves formation of 1,4-butanediones [85JC-S(CC)420; 87JCS(P1)559; 88TL3703; 89JOC2605], followed by treatment with phosphorus pentasulfide. This approach is especially useful for the synthesis of 3,2' : 5',3"-terthiophene (**134**) starting from 1,4-diketone **65** (85SC789).



Carbenoids generated from the catalytic decomposition of phenyliodonium bis(phenylsulfonyl)methylides (**135**) in the presence of thiobenzophenones lead to the formation of benzo[*c*]thiophenes **136** [94JCR(S)2] (Scheme 38). The earlier work [89JCS(P1)379] reporting the synthesis of isomeric benzo[*b*]thiophenes from this reaction was found to be in error.



SCHEME 38



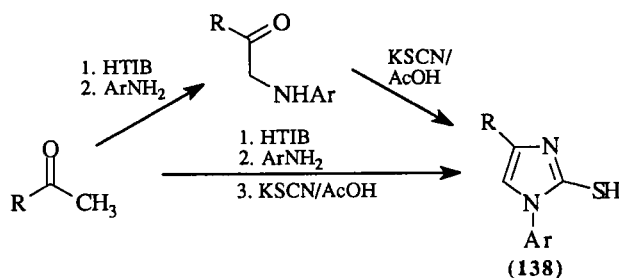
SCHEME 39

Heterocyclic-fused[c]thiophenes **137** can also be synthesized using this approach (Scheme 39) (95S87).

#### 4. Imidazoles and Benzimidazoles

Ready access to  $\alpha$ -aminoketones [92IJC(B)349] via the HTIB-mediated approach has offered a superior alternative to the most widely used Marckwald's synthesis (1892CB2354) of 2-mercaptoimidazoles **138** (Scheme 40). This synthesis can be accomplished by following two experimental procedures involving single or multisteps as outlined in Scheme 40. This method is applicable to the synthesis of 4-(2-thienyl)imidazoles (**138**, R = 2-thienyl), as well [94IJC(B)116].

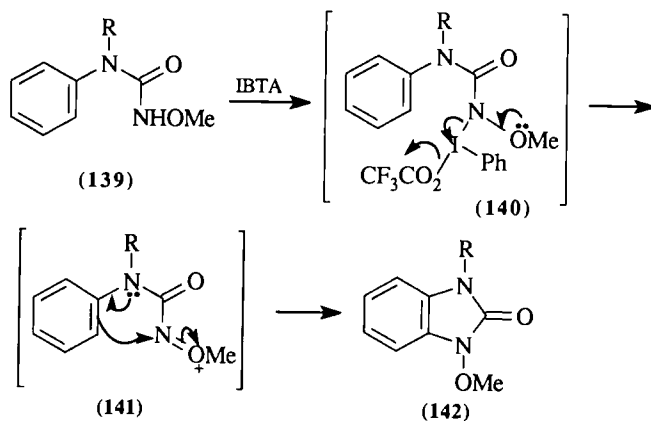
A facile method for the synthesis of *N*-substituted 2-benzimidazolinones **142** has been developed by Romero *et al.* (96TL2361) using *N*-substituted ureas **139**, which are cyclized to **142** with IBTA as an oxidant. The reaction probably proceeds via intermediates **140** and **141**. Besides the *N*-alkyl or aryl substituent, presence of the 1-methoxy group is necessary for the success of this cyclization. Another benzimidazoles synthesis involves cyclization of *N*-phenyl-*C*-alkyl formimidamides with IBD [95JCS(P1)615]



R = Ph, 4-substituted phenyl, 2-thienyl

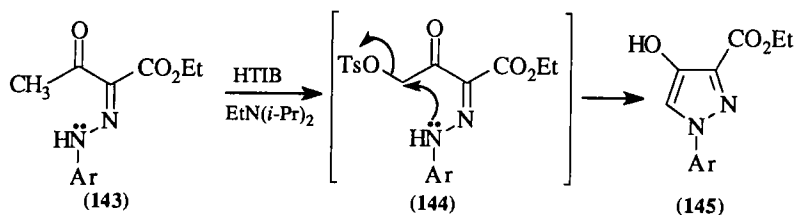
Ar = Ph, 4-substituted phenyl

SCHEME 40

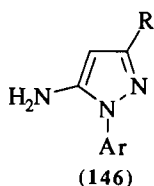


### 5. Pyrazoles

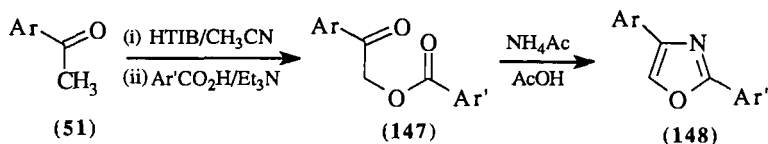
Oxidation of arylhydrazones **143** with HTIB in the presence of diisopropylethylamine produces pyrazoles **145** in one pot. The intermediate  $\alpha$ -tosyloxy compounds **144**, which are generated *in situ* by the oxidation of **143**, undergo intramolecular participation of amino group in displacement of the tosyloxy group, thereby yielding cyclized products **145** (91SC1583).



$\alpha$ -Cyanoketones, which are readily accessible through the HTIB-mediated oxidative approach (87MI1), can offer a new way of synthesizing 5-aminopyrazoles of general formula **146**.





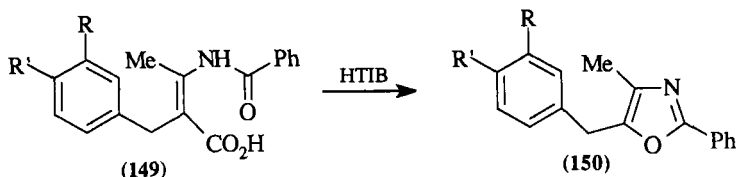


SCHEME 41

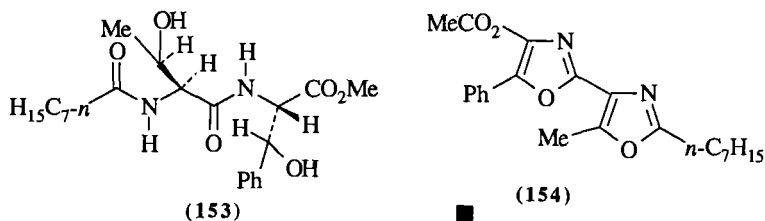
## 6. Oxazoles and Related Compounds

Several synthetic routes are available for oxazoles and related compounds. The first one, outlined in Scheme 41, is based on previously discussed syntheses of benzofurans (Scheme 17) and imidazoles (Scheme 40). Thus,  $\alpha$ -aryloxyacetophenones (**147**), which are obtained by HTIB-induced oxidation of **51** followed by treatment with *para*-substituted benzoic acids, can be cyclized to oxazoles **148** (95JIC129) (Scheme 41).

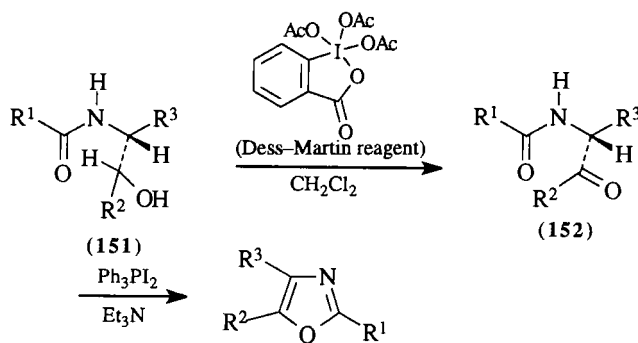
In the second method, oxazoles **150** have been prepared in good yields by HTIB-induced ring closure of enamine carboxylic acids **149** [91JCR(S)302].



Another approach to the synthesis of functionalized oxazoles and bis-oxazoles involves side-chain oxidation of  $\beta$ -hydroxyamides **151** with the Dess—Martin reagent (91JA7277; 93JOC2899), followed by a mild cyclodehydration of the  $\beta$ -keto amides **152** (93JOC3604) (Scheme 42). This methodology can be applied for the preparation of poly-oxazole segments, which are a common feature of several recently isolated biologically active natural products (88JOC5014; 89JOC1360; 91JA2303, 91JA3173). Dipeptide **153**, for instance, is directly converted to the bis-oxazole **154** in 37% yield.



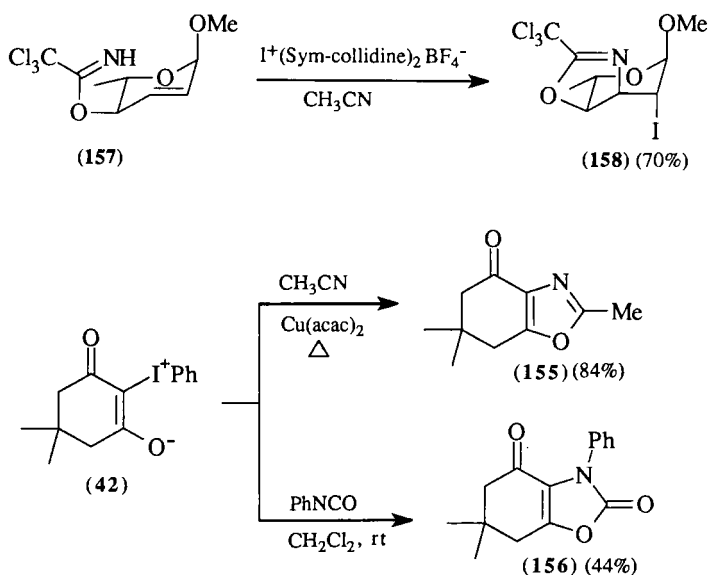
Cycloaddition reactions involving thermal/photochemical/catalytic decomposition of iodonium ylides are applicable to oxazole derivatives



SCHEME 42

(93JOC4885). For example, decomposition of dimedone iodonium ylide (**42**) in the presence of acetonitrile and phenyl isocyanate provides 4,5,6,7-tetrahydrobenzoxazoles **155** (87TL4449) and **156** (75JOC1166), respectively (Scheme 43).

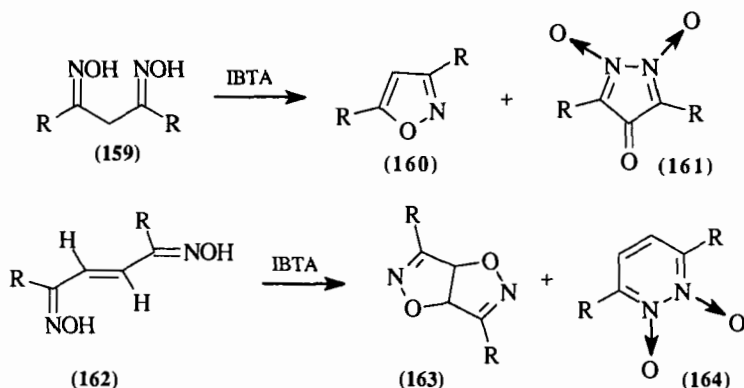
Iodo-oxazoline derivative **158**, which is used in the synthesis of L-daunosamine and related amino sugars, has been synthesized by oxidative cyclization of trichloroacetimidate **157** [88JCS(P1)111].



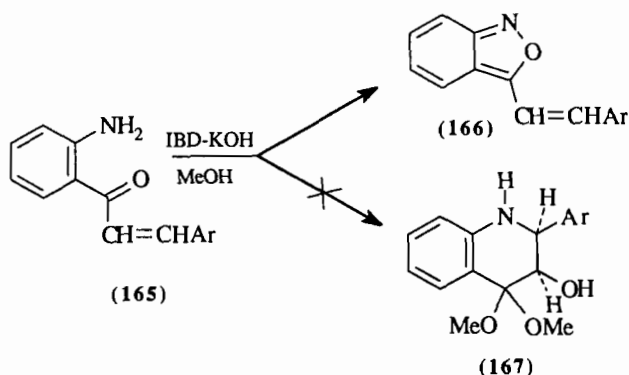
SCHEME 43

## 7. Isoxazoles and Related Compounds

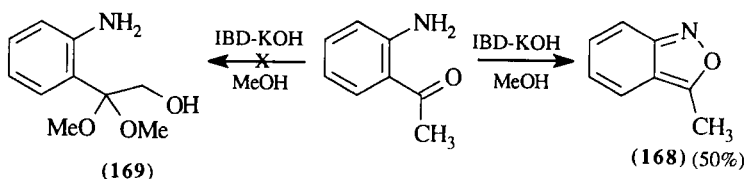
Dioximes are known to generate isoxazoles and related compounds when oxidized with IBTA. However, these reactions are of limited use because of formation of side products. For example, oxidation of dioximes of  $\beta$ -diketones **159** gives rise to a mixture of 3,5-disubstituted oxazoles **160** and pyrazole-di-*N*-oxides **161** (82MI1). In another case, oxidation of dioximes **162** affords a mixture of the isomeric dihydroisoxazolo-isoxazoles **163** and pyridazine dioxides **164** (76S837; 79JOC3524; 82MI1).



Synthesis of 3-( $\beta$ -styryl)-2,1-benzisoxazoles **166** has been accomplished by using a novel oxidative cyclization of *o*-aminochalcones **165** with IBD-KOH/MeOH (97TL3147) (Scheme 44). *o*-Aminoacetophenone under similar conditions also gives analogous product **168** (Scheme 45). Interestingly,



SCHEME 44

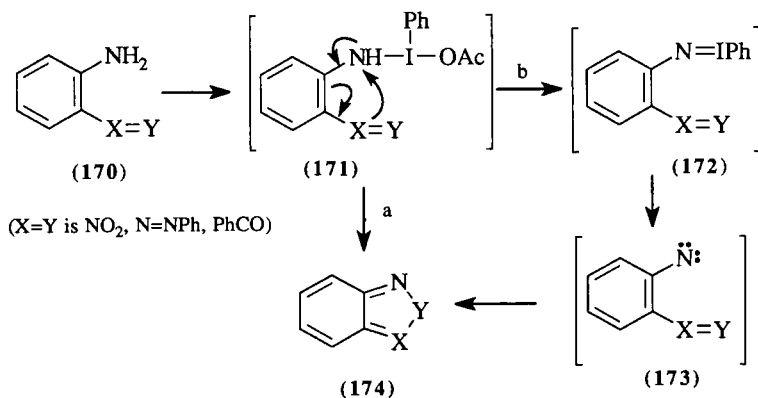


SCHEME 45

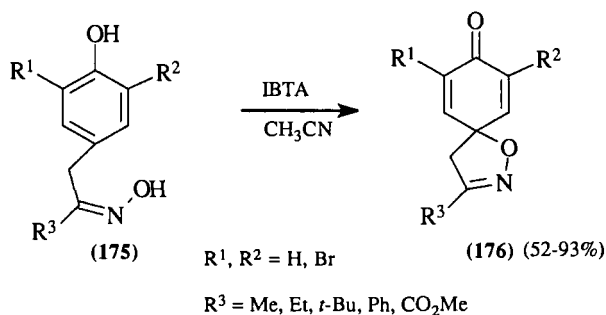
the  $\alpha$ -positions of carbonyl compounds remain unaffected as normal products of such reactions, that is,  $\alpha$ -hydroxydimethylacetals **167** [84JCS(CC)927; 85JOC151; 86ACR244] and **169** (84TL4745) were not isolated even in trace amounts.

A similar cyclization occurs when *o*-substituted anilines **170** are treated with IBD in benzene [54JCS4499; 70JCS(B)636; 73AJC1969, 73AJC2665]. The chalcones **165** and *o*-aminoacetophenone under similar conditions, however, give complex mixtures. A common mechanistic scheme suggested to these oxidative cyclizations involves electrophilic attack of  $I^{(III)}$  reagent at the amino group to give intermediate **171**, which by neighboring group participation undergoes cyclization to the products **174** (Scheme 46, route "a"). The possibility of an alternative route (Scheme 46, route "b") involving nitrene intermediate **173** generated by the decomposition of ylide **172**, can also be considered.

Spiro-isoxazoles **176** are obtained when oximinophenols **175** are oxidized with IBTA in nonnucleophilic solvents such as acetonitrile [93JCS(P1)1771; 94JCS(CC)443] (Scheme 47). This conversion proceeds via oxidation of the phenolic group (see Scheme 5), followed by intramolecular participation in the oximino group.



SCHEME 46

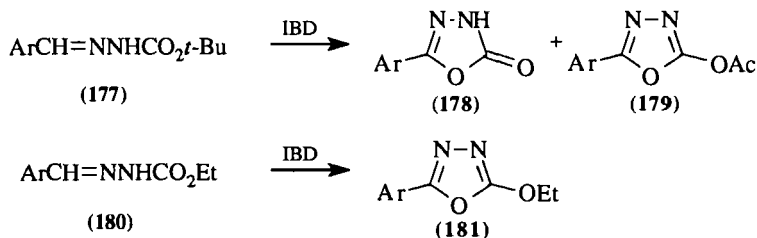


SCHEME 47

## 8. Oxadiazoles and Related Compounds

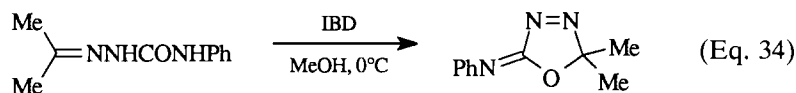
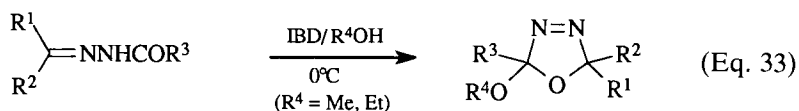
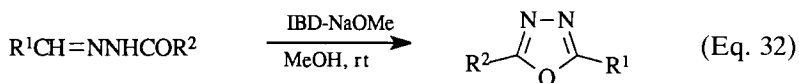
5-Substituted-1,3,4-oxadiazolin-2-ones **178** are synthesized by the oxidation of carbo-*t*-butoxyhydrazones **177** of aromatic aldehydes with IBD. In some cases, in addition to **178**, 5-acetoxy-1,3,4-oxadiazoles **179** are also obtained. The oxidation of ethoxycarbonyl hydrazones **180** affords 2-ethoxy-1,3,4-oxadiazoles **181** (86JHC945) (Scheme 48).

In a related study, it has been shown that several aldehyde *N*-acylhydrazones undergo oxidative cyclization with IBD in methanolic sodium acetate to give 2,5-disubstituted 1,3,4-oxadiazoles (Eq. 32). The oxidation of ketone *N*-acylhydrazones by IBD in methanol or ethanol affords the corresponding 2-alkoxy- $\Delta^3$ -1,3,4-oxadiazolines in excellent yields (Eq. 33), while oxidative cyclization of acetone 4-phenylsemicarbazone provides 2-(*N*-phenylimino)- $\Delta^3$ -1,3,4-oxadiazoline in 93% yield (Eq. 34) (93JOC3381).

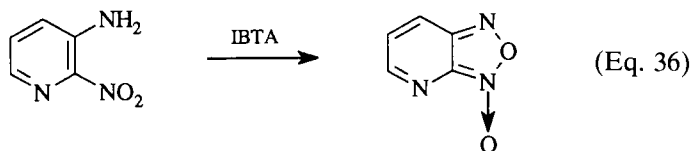
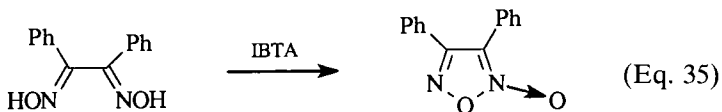


Ar = Ph, 2-ClC<sub>6</sub>H<sub>4</sub>; 2-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>; 4-*i*-PrC<sub>6</sub>H<sub>4</sub>; PhCH=CH; 2-naphthyl; 2-furyl; 4-pyridyl

SCHEME 48

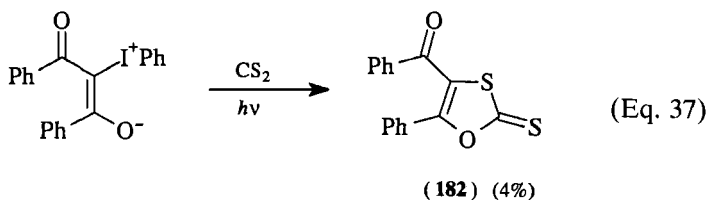


Dioximes of  $\alpha$ -diketones such as benzil on oxidation with IBTA are converted into 1,2,5-oxadiazole-*N*-oxides (furoxans) in high yields (75S445) (Eq. 35). Benzo- (Scheme 46) and pyrido-oxadiazoles (Eq. 36) are formed when *o*-nitroaniline and 3-amino-2-nitropyridine are subjected to similar oxidation.



## 9. Oxathioles and Related Compounds

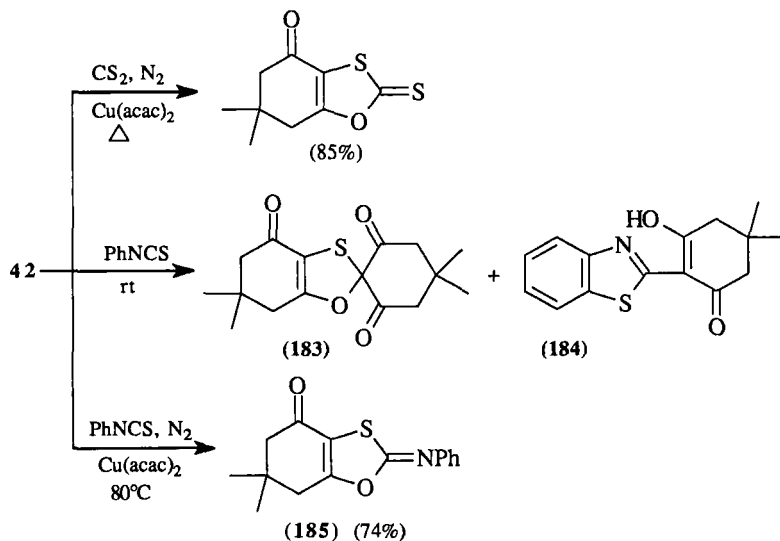
Iodonium ylide-based cycloaddition reactions, employed earlier for furans, oxazoles, and so forth, can be extended to the synthesis of various oxathiole derivatives. The photochemical reaction of dibenzoylmethane iodonium ylide, for instance, undergoes cycloaddition reaction with  $\text{CS}_2$  to give oxathiole **182** (Eq. 37). Further examples of similar oxathioles syntheses are outlined in Schemes 49 and 50 (76JOC125; 85JOC1509; 87TL4449). Reaction conditions can influence the course of these reactions. For example, the reaction of ylide **42** with phenyl isothiocyanate at room temperature gives a mixture of the spiro-oxathiole **183** and benzothiazole derivative **184**, whereas in the presence of  $\text{Cu}(\text{acac})_2$ , the same reactants afford the benzoxathiole **185** (87TL4449).



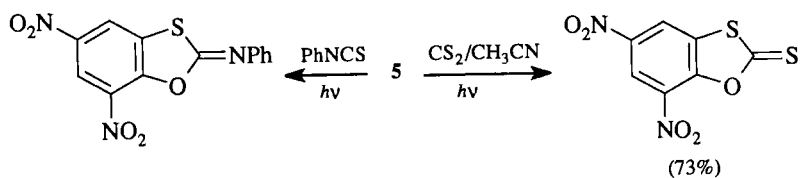
## 10. *Thiazoles and Selenazoles*

2-Amino- (and substituted amino) (187), 2-alkyl/aryl- (188), and 2-substituted hydrazino- (189) thiazoles are obtained by the condensation of  $\alpha$ -tosyloxyketones (186) with thiourea (and substituted thioureas), thioamides, and thiosemicarbazones, respectively [91MI1; 92MI2; 92S845; 95IJC(B)660]. These syntheses provide a useful modification of the well-known Hantzsch thiazoles synthesis (1887CB3118; 1888CB938) and can be performed by using one-pot procedures starting from the corresponding ketones. Using selenourea in place of thioureas, and so on, this approach affords 2-aminoselenazoles 190 (Scheme 51).

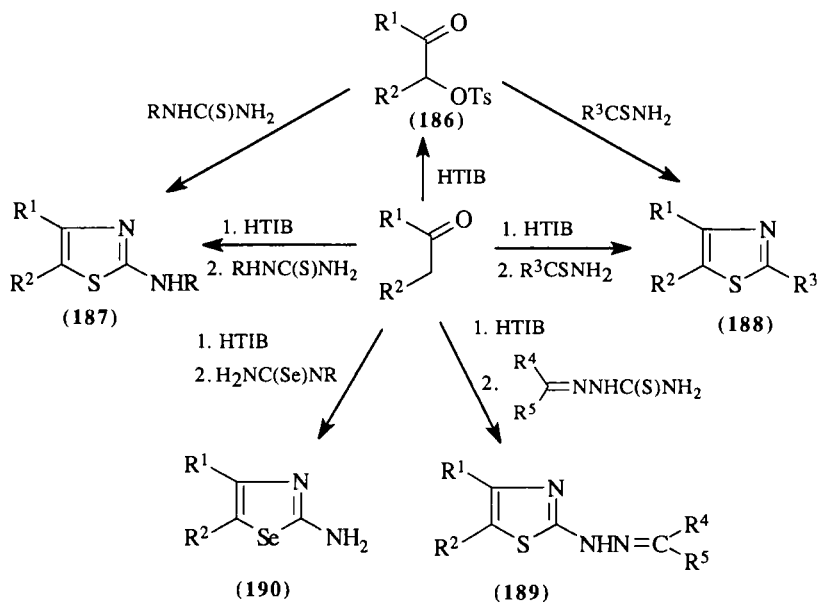
Other examples of thiazoles syntheses include conversion of 51 into 2-hydroxy- (192) and 2-mercapto- (193) thiazoles (93SC1455) (Scheme 52). It is also possible to obtain 192 and 193 in one pot without isolating the intermediate  $\alpha$ -thiocyanoacetophenones (191).



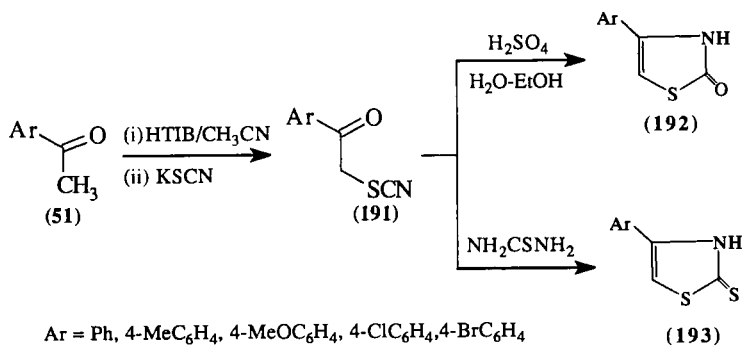
SCHEME 49



SCHEME 50

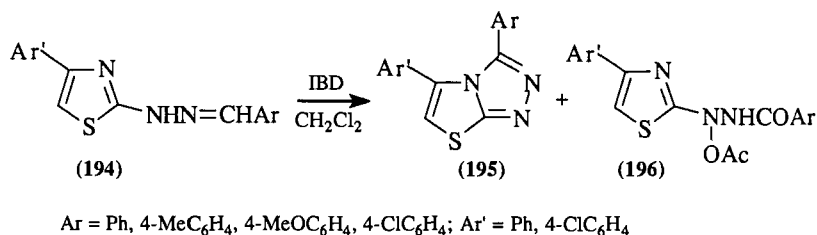


SCHEME 51



SCHEME 52





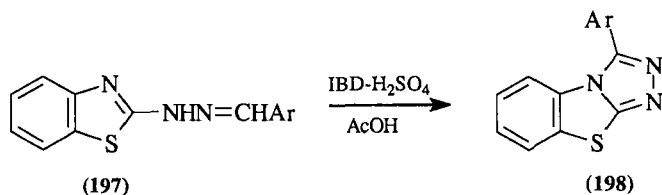
SCHEME 53

## 11. Bridgehead Heterocycles

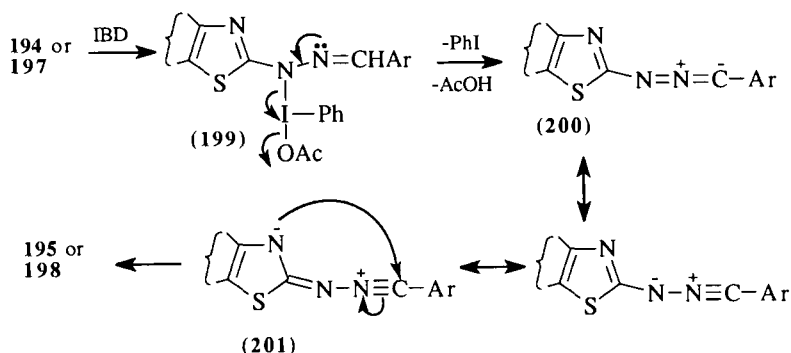
Several 2-thiazolyl- (**194**) and 2-benzothiazolyl- (**197**) hydrazones of aromatic aldehydes undergo oxidative intramolecular cyclization to form 1,2,4-triazolo-bridgehead heterocycles **195** (95SC3363) (Scheme 53) and **198** [93JCR(S)244] (Scheme 54), respectively. In the case of **194**, 1-acetoxy,1-(4-aryl-2-thiazolyl)-2-arylhiazines (**196**) are formed as minor products (Scheme 53).

A common mechanistic scheme has been proposed to the syntheses of **195** and **198** (Scheme 55). The first step is the formation of intermediate **199**, which subsequently loses a molecule of iodobenzene and acetic acid to give nitrilimine intermediate **200**. The nitrilimine **200** via **201** can undergo intramolecular cyclization, thereby yielding the products.

A general scheme, which constructs the thiazolo variety of various bridgehead heterocycles, is basically an extension of HTIB-mediated modification of Hantzsch thiazole synthesis (Scheme 51). Thus, synthesis of 3-substituted-5,6-dihydro-4*H*-imidazo[2,1-*b*]thiazoles **202** has been achieved by the treatment of  $\alpha$ -tosyloxyacetophenones (generated by the oxidation of **51** with HTIB) with ethylenethiourea [92JCS(P1)707]. The method is successfully extended to synthesize 4,5,6,7-tetrahydrothiazolo[3,2-*a*]pyrimidines **203**



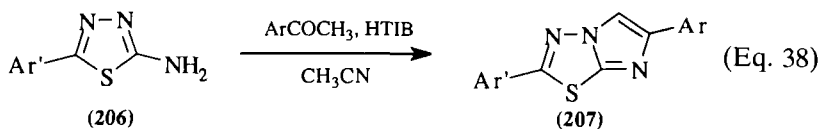
SCHEME 54



SCHEME 55

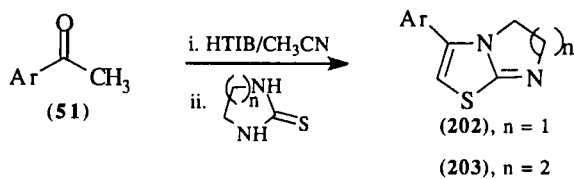
(92SC1293) (Scheme 56). A similar approach provides 3-phenylthiazolo[3,2-a]benzimidazole (**205**) via isolation of intermediate **204** [92JCS(P1)707] (Scheme 57).

$\alpha$ -Tosyloxyacetophenones, generated *in situ* by HTIB-induced oxidation of acetophenones, also find use in building imidazole rings of several novel heterocyclic systems containing bridgehead nitrogen atoms [94IJC(B)686, 94JCR(S)38]. For example, a one-pot synthesis of 2,6-diaryl[2,1-*b*]-1,3,4-thiadiazoles **207** has been reported by the treatment of 2-aminothiadiazoles **206** with acetophenones in the presence of HTIB (Eq. 38).



IBD and 2-nitroiodobenzene diacetate in solvents of low nucleophilicity such as  $\text{CF}_3\text{CH}_2\text{OH}$  cause cyclization of secondary amines in which nitrogen is linked with two nitrogen-containing rings (85TL2723; 86JA8002; 90JA3125) (Scheme 58). The imidazole system of the conversion **208** to **210** is possibly generated by intramolecular cyclization of the initially formed intermediate **209**. This oxidative cyclization is especially useful for the synthesis of covalently linked double-helical cross-sections representative of purine–pyrimidine, purine–purine, and pyrimidine–pyrimidine duplexes (90JA3125).

Another important example of oxidative cyclization leading to bridge-head heterocyclic compound is the conversion of indole derivative **211**

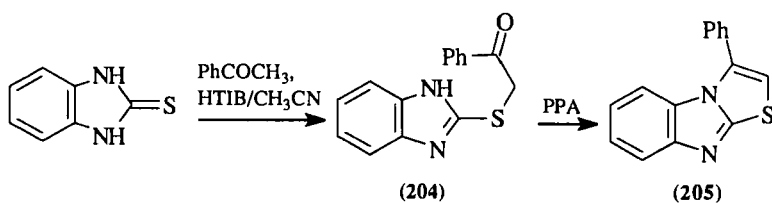


202; Ar = Ph, 4-MeC<sub>6</sub>H<sub>4</sub>, 4-MeOC<sub>6</sub>H<sub>4</sub>, 4-ClC<sub>6</sub>H<sub>4</sub>,

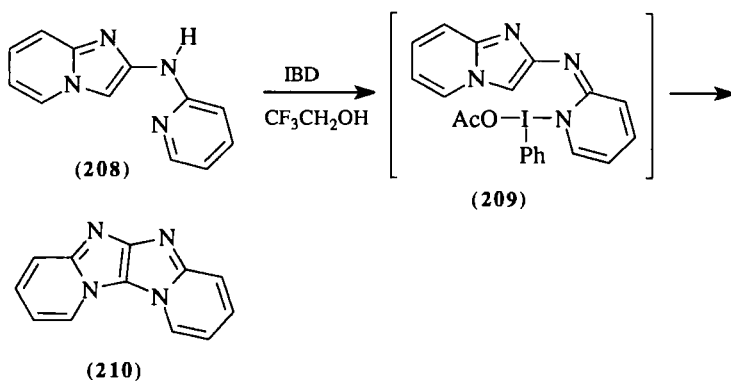
4-BrC<sub>6</sub>H<sub>4</sub>, 4-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>

203; Ar = Ph, 4-ClC<sub>6</sub>H<sub>4</sub>, 4-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>, 4-C<sub>6</sub>H<sub>5</sub>C<sub>6</sub>H<sub>4</sub>

SCHEME 56

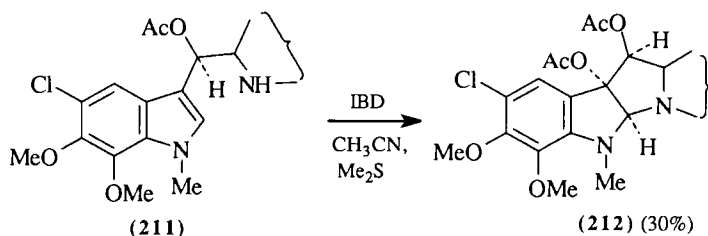


SCHEME 57



SCHEME 58

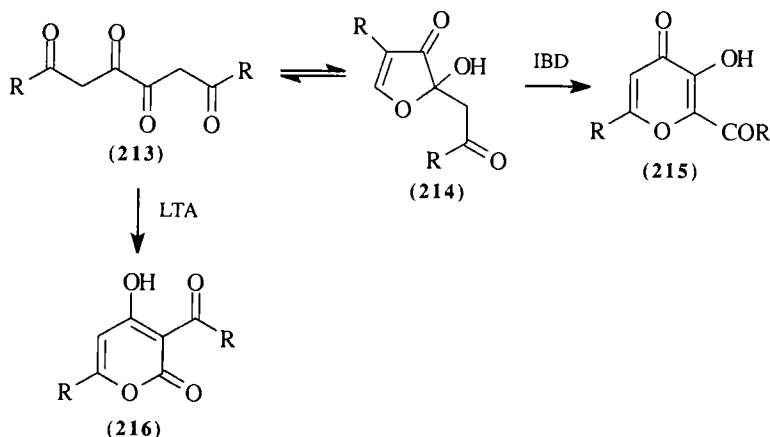
into **212**, which has been used in the total synthesis of sporidesmin-A (73JA6493).



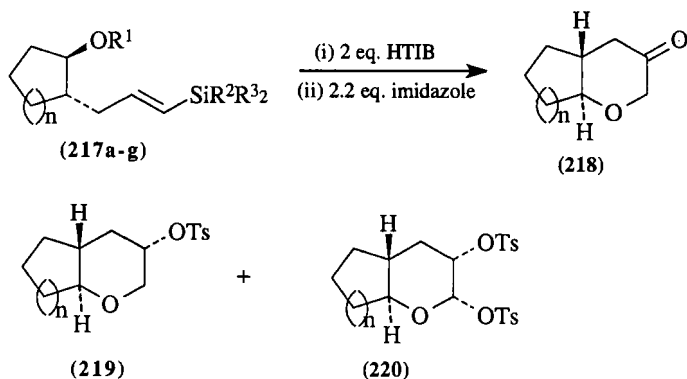
### E. SIX-MEMBERED RING HETEROCYCLES

#### 1. Pyrones, Benzopyrans, etc.

On treatment with IBD, tetraketones **213** are transformed to pyrones **215**. This reaction probably occurs via intermediate cyclic ene-hemiacetal **214**. In contrast, lead tetra-acetate (LTA), which generally behaves similarly to IBD, shows a different reactivity pattern in the oxidation of **213**, thereby yielding the isomeric pyrone **216** (80TL1575; 83JHC1389).



In another study, the silyl-substituted  $\delta$ ,  $\epsilon$ -unsaturated alcohols **217** undergo ring closure to give reduced pyran-3-ones **218**, as well as tosyloxy-substituted tetrahydropyrans **219** and **220** [90JCS(P1)1481]. In case of alcohols **217f–g**, phenyl substituents have been used to assess the effect of electron-withdrawing substituents on the regiochemistry of ring closure (Scheme 59). Apparently, the diphenylmethylsilyl group also leads to the

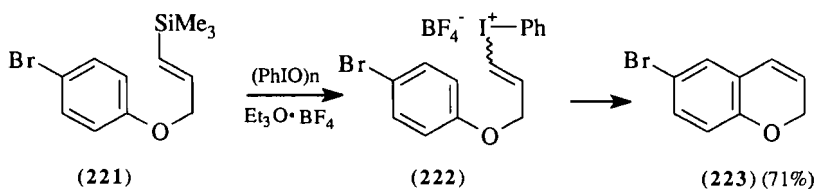


Substrate					Product ratio			
217	n	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	218	219	220	Total % yield
a	1	H	Me	Me	10	1	1	15
b	2	H	Me	Me	3	1	0.5	87
c	2	Me	Me	Me	3	1	0.5	68
d	2	Bn	Me	Me	3	1	0.5	56
e	2	SiMe <sub>2</sub> Thex	Me	Me	3	1	0.5	51
f	2	H	Me	Ph	5	0.4	0.4	51
g	2	H	Ph	Ph	--	--	--	62

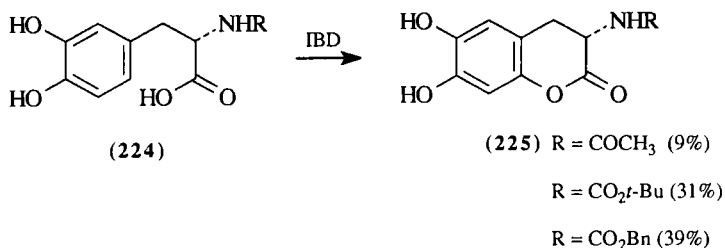
SCHEME 59

same products as trimethylsilyl substituents in **217a-e**, although the preference for **218** is more pronounced in **217f-g**. In contrast, exclusive formation of tetrahydrofurans **84** from triphenylsilyl-substituted alkenol **83** (see Section II,D) has been observed.

6-Bromo-2*H*-chromene (**223**) is conveniently prepared by intramolecular cyclization of iodonium salt **222**. The latter is obtained by the oxidation of alkenyltrimethylsilane **221** with iodosobenzene [86JCS(CC)1382].

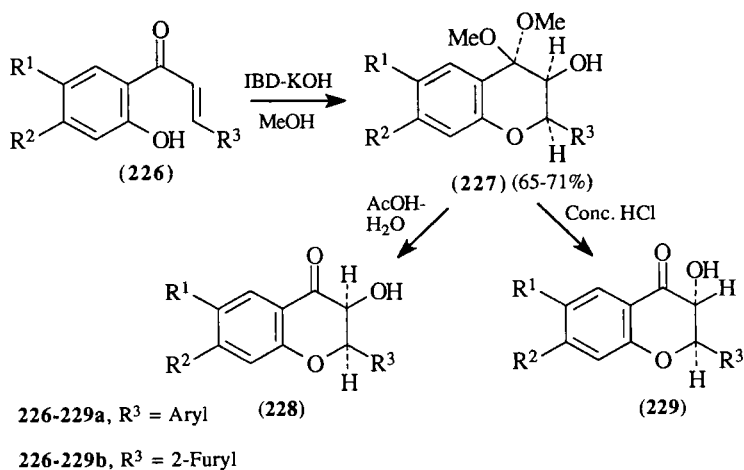


*N*-Acyl-3-(3,4-dihydroxyphenyl)-L-alanines (**224**) on oxidative cyclization provide a one-step synthesis of 3,4-dihydrocoumarins **225** (70HCA1708). This example, in fact, is based on oxidative cyclization of phenols.

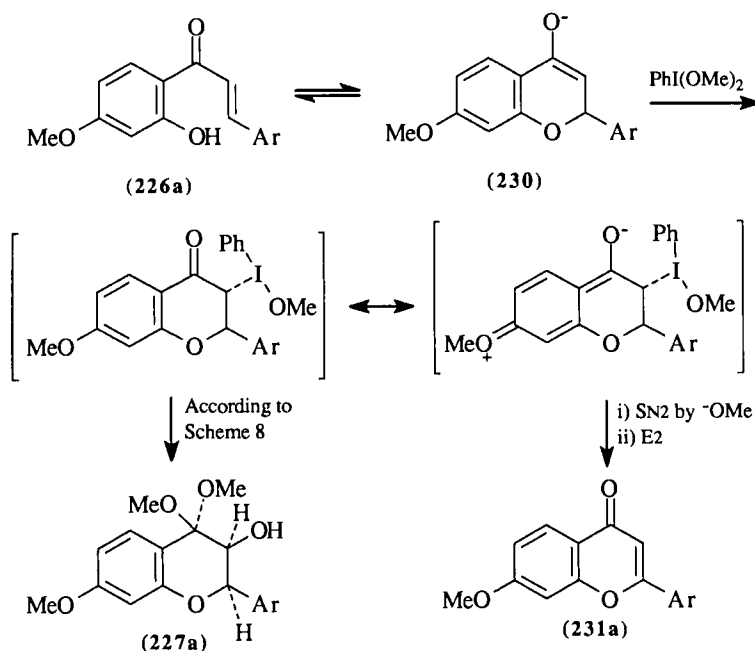


The reaction of  $\alpha$ -hydroxydimethylacetal formation (Scheme 1a) has introduced a novel approach for the synthesis of relatively less established *cis*-3-hydroxyflavanones (**228**). Thus, oxidation of *o*-hydroxychalcones **226a** and 2-furyl analogs **226b** affords *cis*-3-hydroxyflavanone dimethylacetals **227a** and corresponding 2-furyl analogs **227b**. The reaction is regio- as well as stereospecific. Acid hydrolysis of these acetals under controlled conditions gives **228**. Strong acidic conditions lead to *trans*-isomers **229** [85JOC151; 91IJC(B)1023; 92SC327] (Scheme 60).

Although conversion **226** to **228** is quite general, the presence of a methoxyl group at the *para* position of ring A of the chalcone **226** changes the course of this process. The chalcone **226a**, for example, on treatment

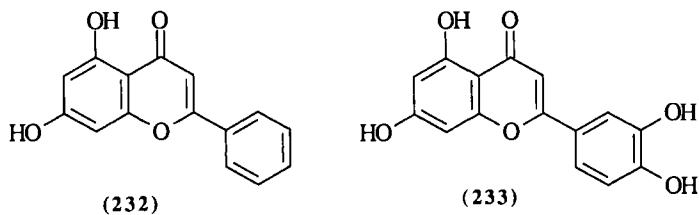


SCHEME 60

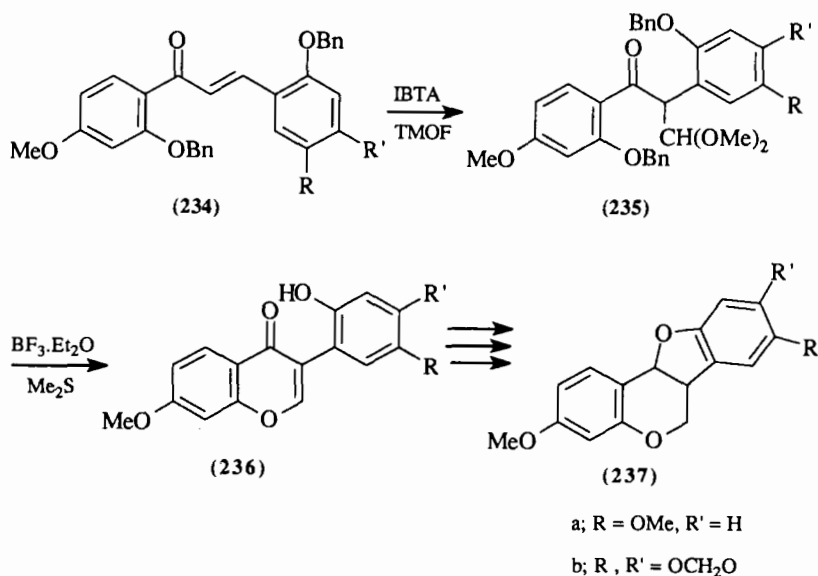


SCHEME 61

with IBD-KOH/MeOH at room temperature produces a mixture of flavone **231a** and normal acetal **227a** in the ratio of 3:1. A mechanistic rationale for these observations is outlined in Scheme 61. Interestingly, extension of this study has offered new syntheses of naturally occurring flavones, namely chrysin (**232**) and luteolin (**233**) (95LA1711).



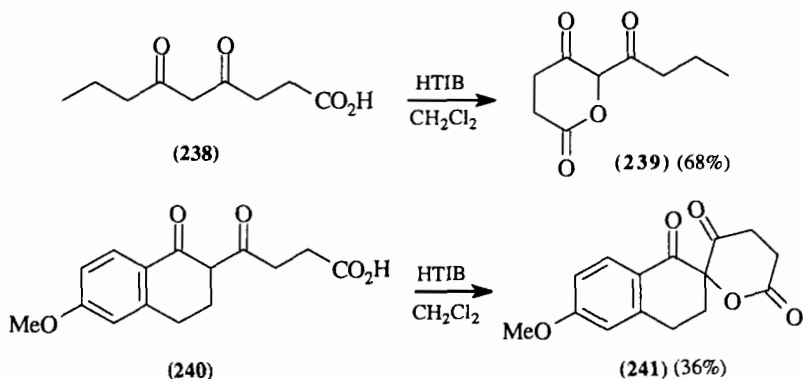
Oxidative rearrangement of chalcones presented in Eq. (2) finds an interesting use in the synthesis of pterocarpans. Thus, reaction of chalcone **234** with IBTA in trimethyl orthoformate (TMOF) in the presence of trifluoroacetic acid affords the corresponding rearrangement product **235** in good yields. Cyclization of **235** with boron trifluoride etherate and dimethylsulfide gives isoflavone **236**, which could be converted into homopterocarpin (**237**;  $\text{R} = \text{OMe}$ ,  $\text{R}' = \text{H}$ ) (94SL1001) (Scheme 62).



SCHEME 62

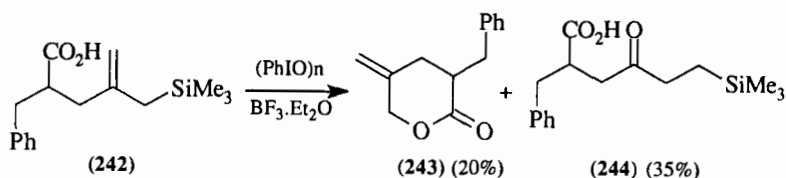
## 2. Lactones and Spirolactones

4,6-Dioxocarboxylic acid **238** upon treatment with HTIB, cyclizes to dioxo- $\delta$ -lactone **239** by intramolecular participation of the carboxylic group. When cyclic diketo acid **240** is the substrate, spirolactone **241** is obtained (90TL201).



The cyclization method of Ochiai *et al.* (85CPB989), used for reduced furans **94**, affords a mixture of six-membered lactone **243** and the rearranged  $\gamma$ -keto acid **244** when acid **242** is the substrate.

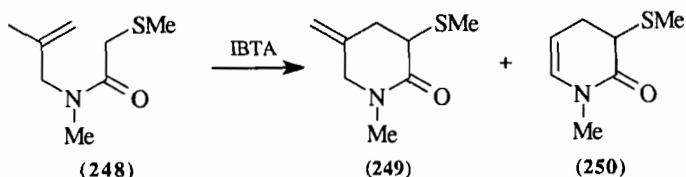




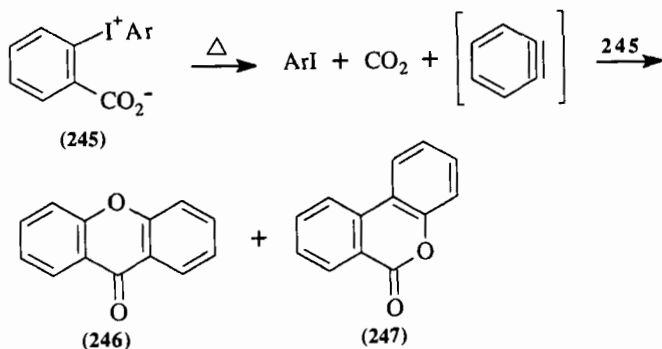
Mixtures of xanthone (**246**) and 3,4-benzocoumarin (**247**) result when 2-aryliodonobenzoates **245** are heated at higher temperature. This reaction involves fragmentation of **245** to benzyne, carbon dioxide, and iodoarene. Thus, in the absence of trapping agents, the benzyne intermediate reacts with **245** to form cyclized products **246** and **247** (64JOC1637) (Scheme 63).

### 3. Piperidines and Related Compounds

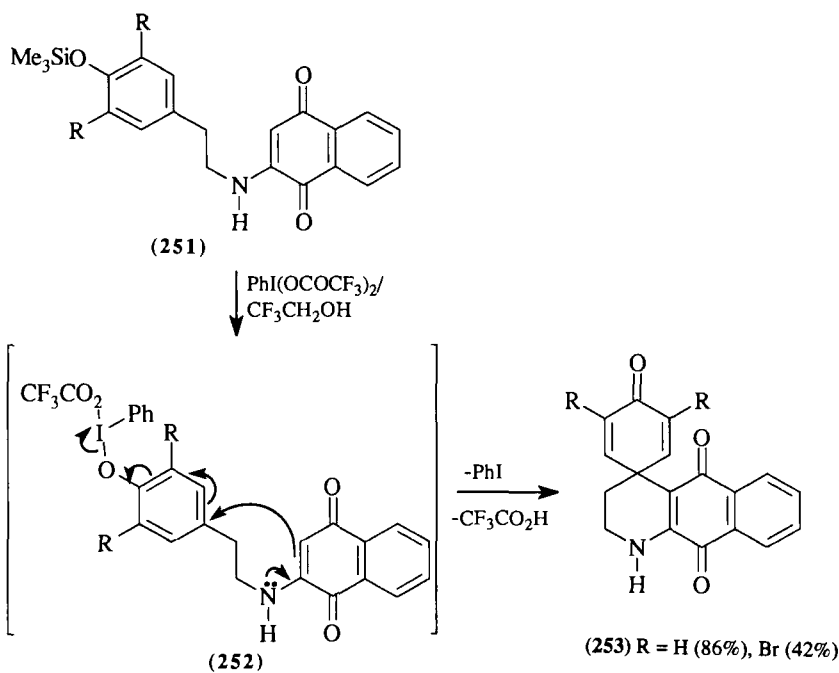
Under Pummerer rearrangement conditions,  $\alpha$ -methylthio amide **248** affords a mixture of 2-piperidone **249** and pyridin-2-(3*H*)-one **250** (86CPB1061).



Intramolecular oxidative coupling of silylated phenols **251** with IBTA leads to the formation of spiropiperidine derivatives **253**, called aza-anthraquinone-spirodienones (89TL1119) (Scheme 64). The first step of this conversion is the electrophilic attack of  $\text{I}^{(\text{III})}$  reagent on the phenolic group to give intermediate **252**. Intramolecular C—C bond formation leads

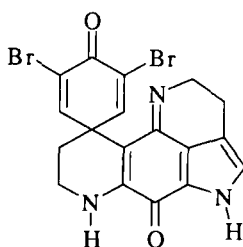


SCHEME 63



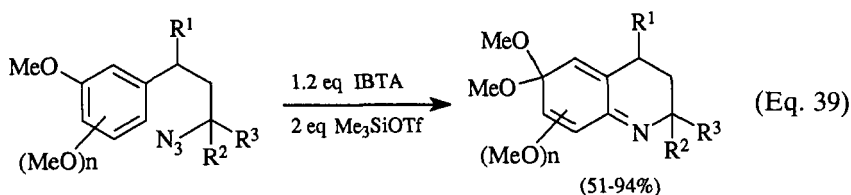
SCHEME 64

to cyclized products **253** along with the expulsion of iodobenzene and trifluoroacetic acid. This reaction has offered a new synthetic approach to the antitumor marine natural product discorhabdin C (91TL2035; 92JA2175).

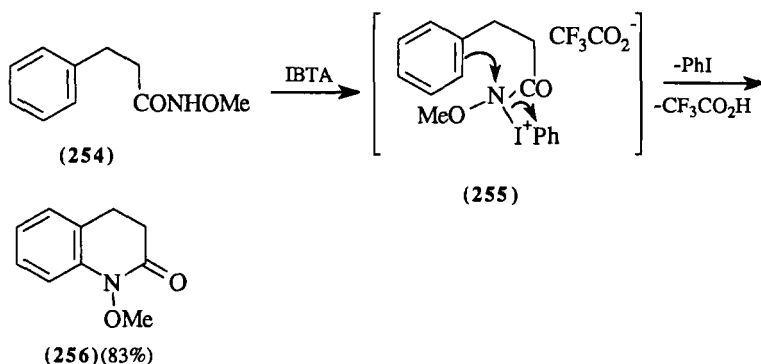


Discorhabdin C

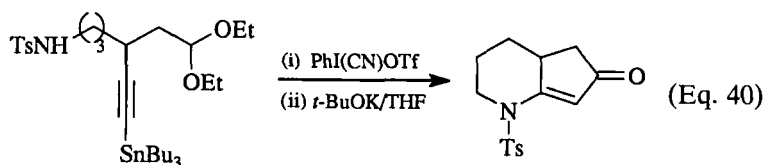
A direct synthesis of cyclic quinone imine acetals has been accomplished by the treatment of substituted phenol ethers bearing an alkyl azido side chain with IBTA (Eq. 39) [96JCS(CC)1491]. The cyclization reaction proceeds smoothly in polar and low nucleophilic solvents such as  $\text{CF}_3\text{CH}_2\text{OH}$  and  $(\text{CF}_3)_2\text{CHOH}$  in the presence of 10% MeOH.



On cyclization with IBTA, *N*-methoxyamides **254** are converted to *N*-methoxytetrahydroquinoline **256**. The reaction proceeds via intermediate **255**, which undergoes intramolecular cyclization to give **256** (90CL581).

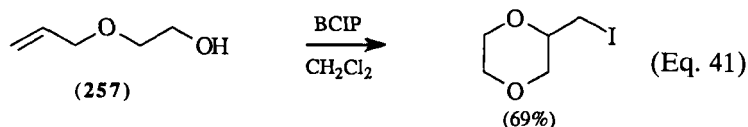


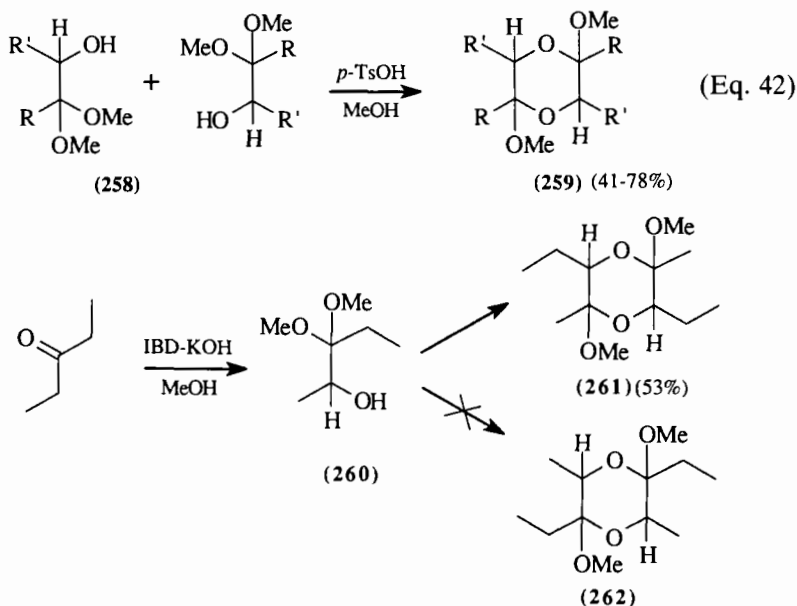
Intramolecular bicyclization of tosylamide with alkynyliodonium salt (see Scheme 31), developed by Feldman and co-workers (95JA7544), is also applicable to the synthesis of *N*-tosylpiperidine derivatives related to polycyclic alkaloids (Eq. 40). Examples leading to seven-membered rings have also been reported.



#### 4. 1,4-Dioxanes

The Evans method (88S862) affords 2-iodomethyl-1,4-dioxane when alcohol **257** is subjected to this cyclization process (Eq. 41).



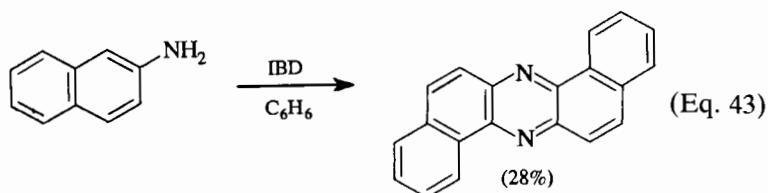


SCHEME 65

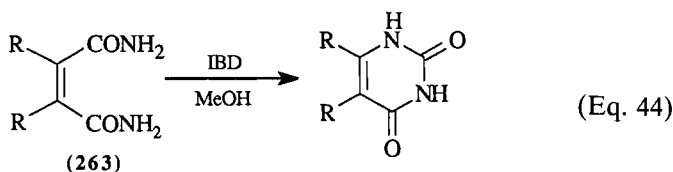
In another approach, several  $\alpha$ -hydroxydimethylacetals **258**, available according to Scheme 1a, undergo bimolecular loss of MeOH under acid catalyst, to yield the corresponding 1,4-dioxanes **259** (84JOC4581) (Eq. 42). In the case of 3,3-dimethoxy-2-pentanol (**260**), which is prepared from 3-pentanone, the cyclization gives dioxane **261** rather than the expected **262** (Scheme 65). The rearrangement of **260** to a mechanistically reasonable precursor of **261** is well known from the work of Creary and Rollin (77JOC4231).

### 5. Diazines

Dibenzophenazine has been synthesized by the oxidation of  $\beta$ -naphthylamine in benzene (53JCS1989) (Eq. 43). In contrast, use of acetic acid as a solvent in this reaction gives 2-acetamido-1,4-naphthoquinone and some unknown product (54JCS3122).

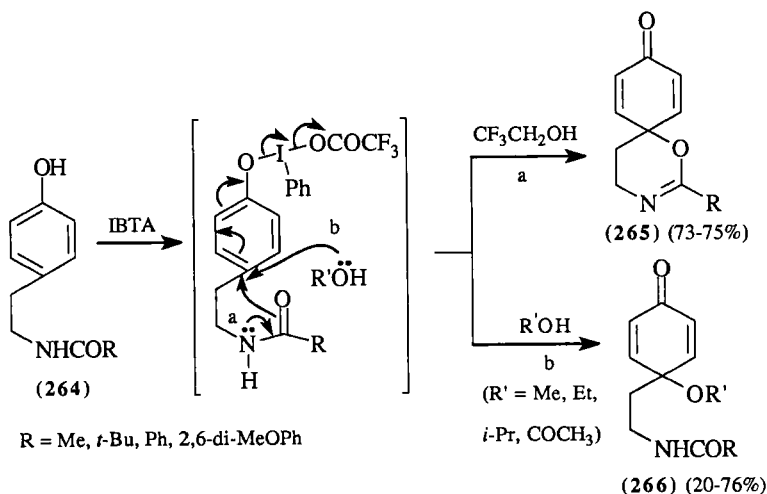


Several diamides of general formula **263** undergo oxidative cyclization with IBD to give pyrimidine derivatives or their benzo-analogs in high yields (90AJC451) (Eq. 44). The first stage of this cyclization is a Hofmann-type rearrangement.



## 6. Spiro-oxazines

Oxidation of *N*-acyltyramines **264** with IBTA proceeds with intramolecular participation of amido group oxygen in nonnucleophilic solvents to give spiro-oxazines **265** (Scheme 66, route "a"). In nucleophilic solvents such as alcohol or acetic acid, addition of solvent at the *para* position occurs to give quinone **266** (Scheme 66, route "b") (91JOC435).

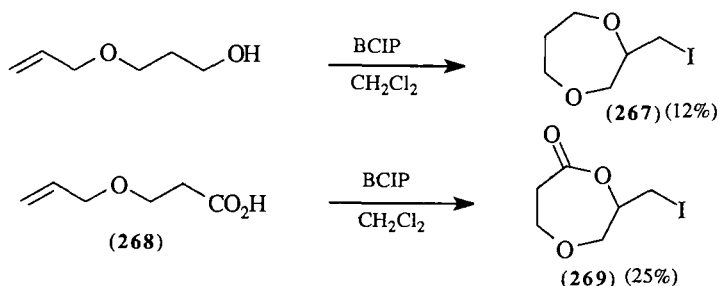


SCHEME 66

## F. SEVEN-MEMBERED RING HETEROCYCLES

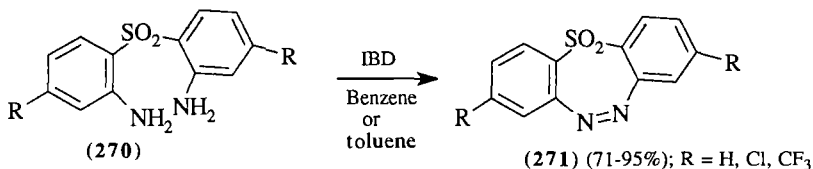
1. *Oxygen Heterocycles*

1,4-Dioxheptane **267** and analogous lactone **269** can be synthesized by using BCIP (88S862). In the case of lactone **269**, unsaturated acid **268** is employed as the substrate.

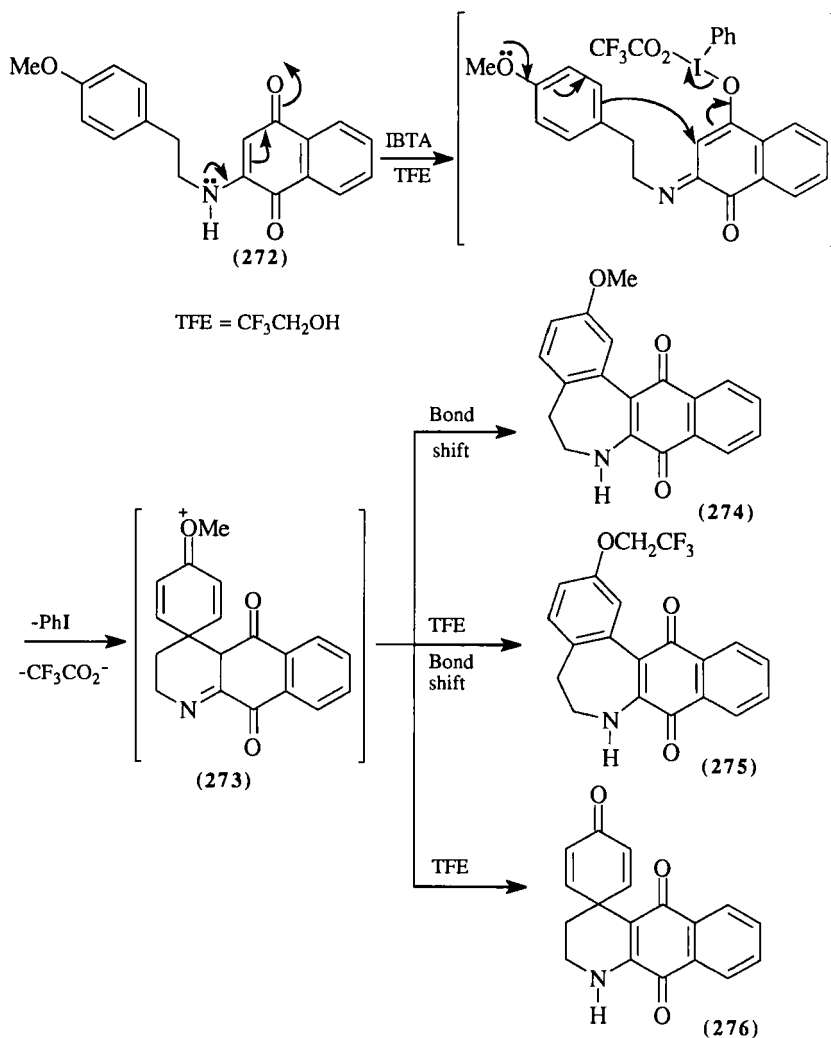
2. *Nitrogen Heterocycles*

Iodoarene diacetates are known to oxidize primary aromatic amines with the formation of azo compounds (53JCS1989; 54JCS3122, 54JCS-4502). Intramolecular azo group formation is a useful reaction for the cyclization of amines **270** to diazepines **271** (56JA458; 61JOC4173) (Scheme 67).

Kita *et al.* found that phenolic oxidative coupling in case of **272** provides seven-membered "N" heterocyclic compounds **274** and **275** by bond shift of the initially formed spiro intermediate **273** under suitable conditions. Besides **274** and **275**, piperidino-spiroquinone **276** is also formed in this oxidation (Scheme 68). Of particular interest is the recently developed synthesis of amaryllidaceae alkaloids such as (+)-maritidine (Scheme 69) (96JOC5857).

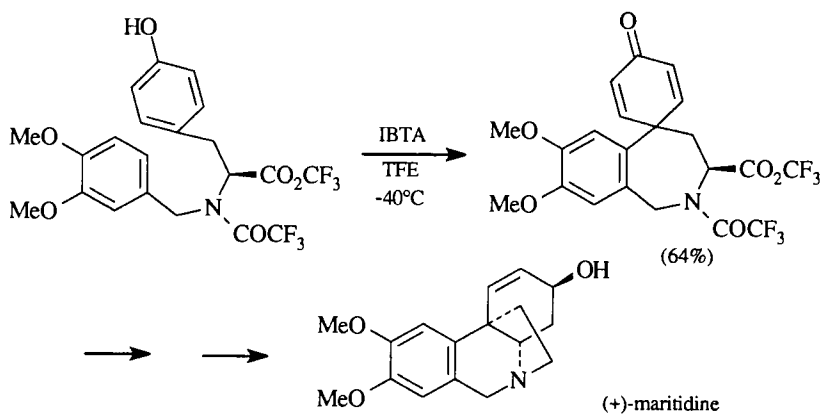


SCHEME 67

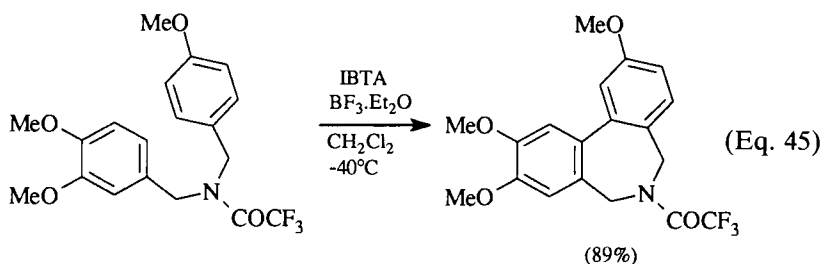


SCHEME 68

Nonphenolic oxidative coupling of phenol ether derivatives using IBTA can also produce seven-membered N-containing heterocyclic compounds as exemplified by Eq. (45) [96JCS(CC)1481].

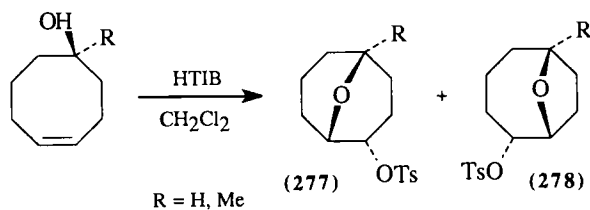


SCHEME 69



### G. MISCELLANEOUS HETEROCYCLIC COMPOUNDS

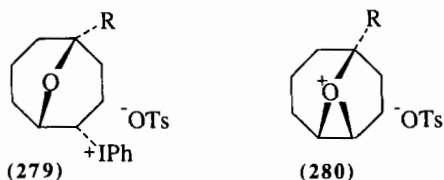
The bicyclic ethers **277** and **278** are obtained by a transannular oxidative cyclization using HTIB. Although this reaction shows poor regioselectivity, the addition to the double bond proceeds with high *trans* stereoselectivity (87TL5229) (Scheme 70).



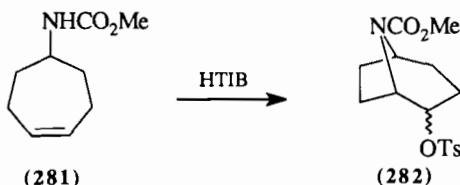
SCHEME 70



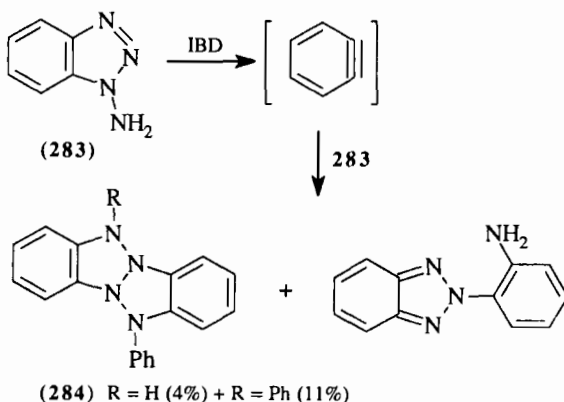
The mechanistic rationale for the high stereoselectivity is provided by the intermediate production of the *trans*-iodonium species **279** and its collapse to the bridged oxonium species **280** prior to the introduction of the toxyloxy ligand.



Similarly, intramolecular participation of nitrogen in the oxidation of carbamates **281** affords bridgehead heterocycle **282** in high yield.

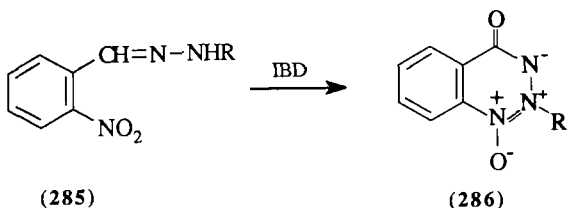


Oxidation of 1-aminobenzotriazole (**283**) among other products results in the formation of bistriazolo compound **284**. This reaction involves a benzene intermediate and illustrates an example wherein IBD behaves differently than lead tetra-acetate, which in this case gives biphenylene [80JCR(S)303] (Scheme 71).



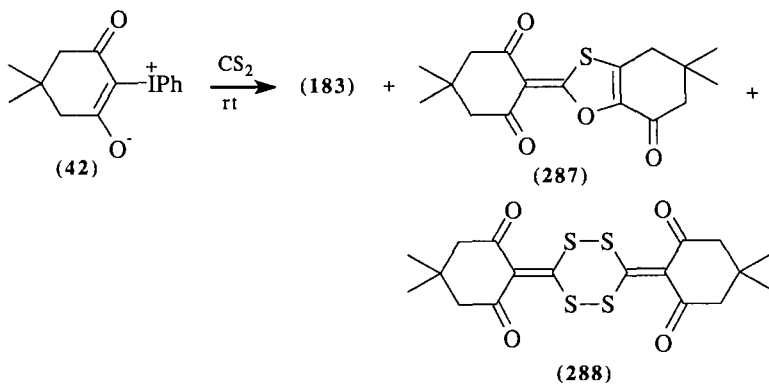
SCHEME 71

Hydrazones **285** are oxidatively cyclized by IBD to form **286**. Similar cyclization is accessible by using lead tetra-acetate as an oxidant, but results are inferior to those with IBD [89JCS(P1)543].



Iodonium ylide **42** on reaction CS<sub>2</sub> at room temperature in the absence of any catalyst or light leads to the formation of a mixture containing three "S" heterocyclic compounds **183**, **287**, and **288** (81KGS1494) (Scheme 72). A tetrathianic heterocyclic compound, analogous to **288**, is obtained in 30% yield by heating phenyliodonium bis(phenylsulfonyl)methylide (**135**, R = Ph) and CS<sub>2</sub> under reflux (85JA7178).

Phenyliodonium sulfate **289**, which is obtained from the reaction of iodosobenzene and sulfur trioxide at -50°C, behaves as a 1,4-dipole in the reactions with several alkenes (86ZOR450) to give intermediate [4 + 2] cycloadduct **290**. Decomposition of this unstable adduct affords cyclic sulfates **291** (Scheme 73). Likewise, another 1,4-dipole **292** undergoes cycloaddition reaction to give cyclic sulfone **293** (88ZOR888). The 1,4-dipole **292** thermally decomposes to give **294** (86DOK1374) (Scheme 74).



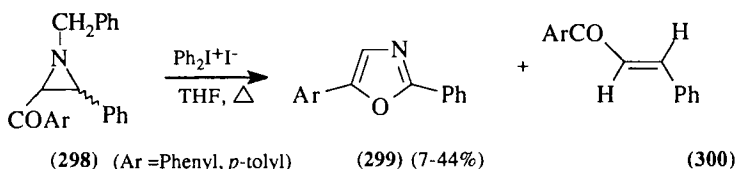
SCHEME 72



### III. Transformations of Heterocyclic Compounds

#### A. AZIRIDINES TO OXAZOLES

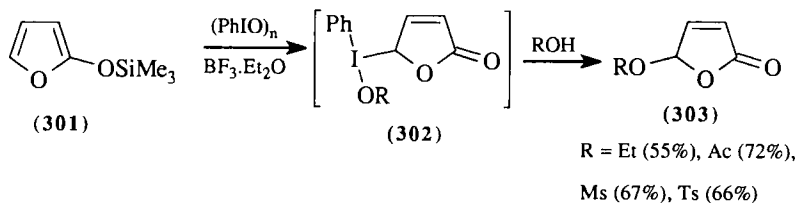
2-Aroylaziridines **298** undergo ring expansion to 2,5-diaryloxazoles **299** by using diphenyl iodonium iodide as an oxidant. Another major product obtained from this reaction is the corresponding  $\alpha,\beta$ -unsaturated ketone **300** (68JOC1317).



#### B. 2-HYDROXYFURANS TO 2(5*H*)-FURANONES

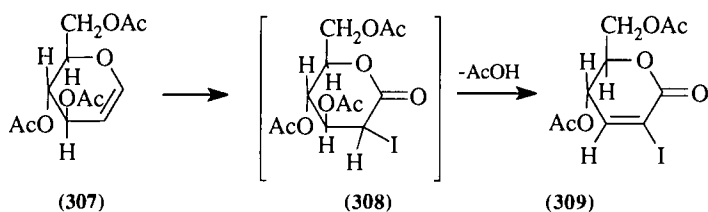
Oxidation of 2-(trimethylsilyloxy)furan (**301**) with iodosobenzene in the presence of boron trifluoride etherate and alcohols or acids results in the formation of 5-substituted 2(5*H*)-furanones **303**. The first step of this conversion gives intermediate **302**, which on nucleophilic substitution by alcohols or acids affords the products (89TL3019) (Scheme 75).

Using trimethylsilyl azide in place of alcohols or acids, 5-azido-2(5*H*)furanone is obtained in 51% yield. Similarly, 2-(trimethylsilyloxy)benzofuran is transformed into 3-acetoxy- (**304a**) and 51% yield. Similarly, 2-(trimethylsilyloxy)benzofuran is transformed into 3-acetoxy- (**304a**) and 3-tosyloxy- (**304b**) 2-coumaranones (Scheme 76).



SCHEME 75



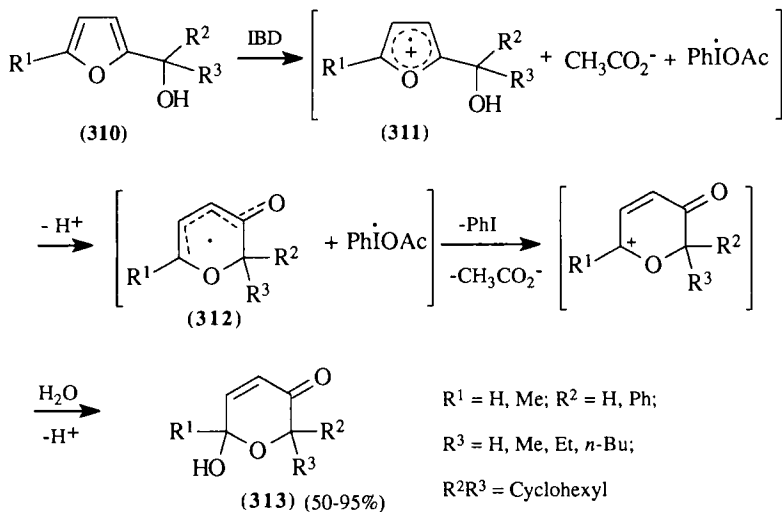


SCHEME 78

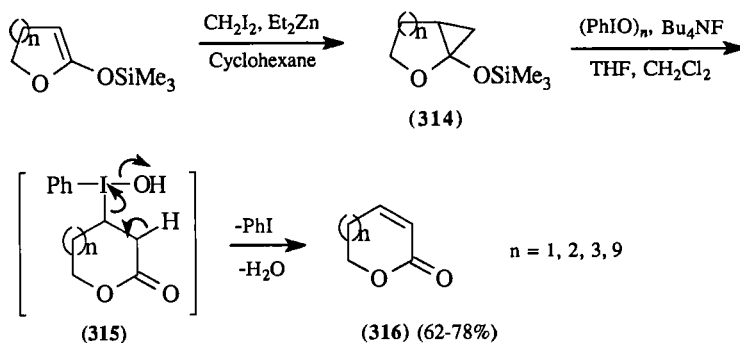
KBF<sub>4</sub>, and methyl viologen considerably enhances the efficiency of this reaction.

### E. LACTONES TO THE HIGHER HOMOLOGOUS $\alpha,\beta$ -UNSATURATED LACTONES

Silyloxypropanols (314) derived from lactones undergo oxidative ring expansion to afford higher homologous  $\alpha,\beta$ -unsaturated lactones (316) (90TL197). The reaction proceeds through the fluoride ion assisted formation of intermediate 315, which on reductive elimination of I<sup>(III)</sup> species yields the product (Scheme 80).



SCHEME 79

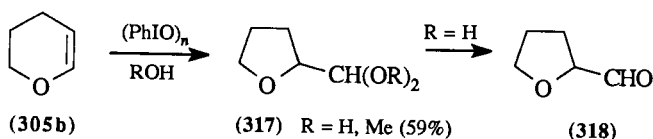


SCHEME 80

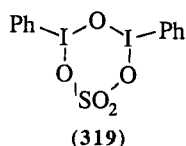
## F. RING CONTRACTION OF DIHYDROPYRAN

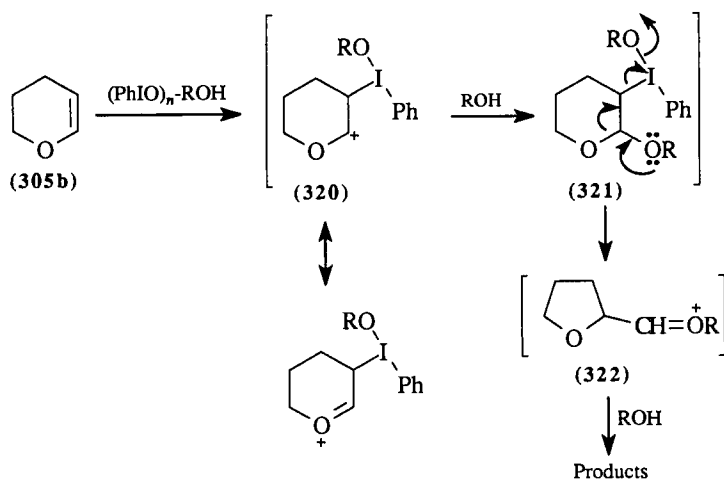
Iodosobenzene in the presence of water or methanol reacts with dihydropyran (**305b**) to give tetrahydrofurfural (**318**) or its dimethylacetal **317** ( $R = \text{Me}$ ), respectively [96JCR(S)432] (Scheme 81). A similar ring contraction occurs when **305b** is treated with cyclic  $\text{I}^{(\text{III})}$  sulfate **319** (88IZV1452).

The mechanism of this transformation presumably involves the formation of cationic intermediate **320**, which is stabilized by resonance. In the second step, nucleophilic attack of the solvent  $\text{ROH}$  gives intermediate **321**, which subsequently undergoes 1,2-shift to yield the products via **322** (Scheme 82).



SCHEME 81





SCHEME 82

### G. CONVERSIONS FROM FLAVANONES

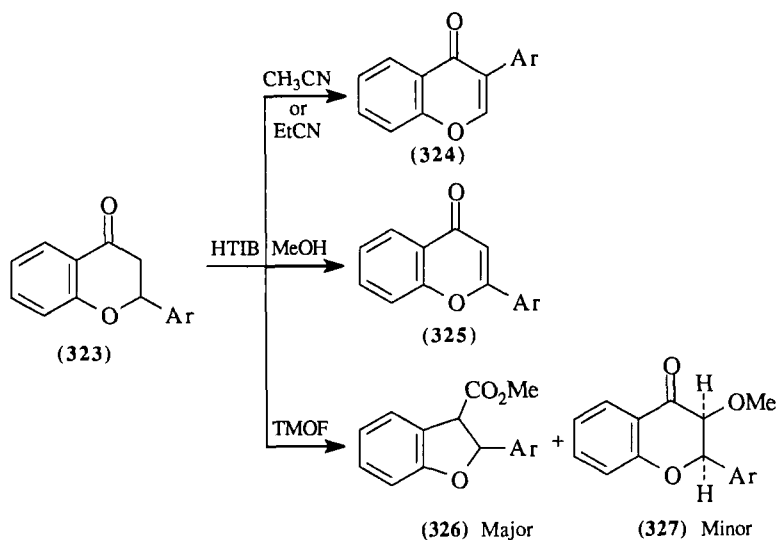
Hypervalent iodine reagents have shown promising applications in the synthesis of flavonoids. Such an example has been covered in Section II,E (Scheme 60). This section deals with various conversions from flavanone substrates.

Depending on the reaction conditions, isoflavones **324** [90SL337; 95JCR(M)1429, 95JCR(S)213], flavones **325** (90SC1417), and methyl 2-aryl-2,3-dihydrobenzofuran-3-carboxylates **291** (95BCJ1168) can be prepared starting from flavanones **323**. As shown in Scheme 83, the course of oxidation of **323** is greatly influenced by the solvent employed. Thus, oxidation with HTIB in boiling acetonitrile or propionitrile affords **324** as the major products, while use of methanol as a solvent gives dehydrogenated products **325**. In contrast, when TMOF is employed as a solvent in these oxidations, a ring contraction occurs with the formation of **326** along with minor amounts of *cis*-methoxyflavonones **327**.

Detailed experimental studies have established that it is possible to choose reaction conditions giving a more selective process. For instance, the other conditions that can yield **324** as the major product from the oxidation of **323** are (i) IBD-*p*-TsOH in acetonitrile, and (ii) iodosobenzene-MsOH in dichloromethane or acetonitrile.

Although substituents present in the flavanones generally do not affect the course of these reactions, the presence of hydroxyl or other oxidizable



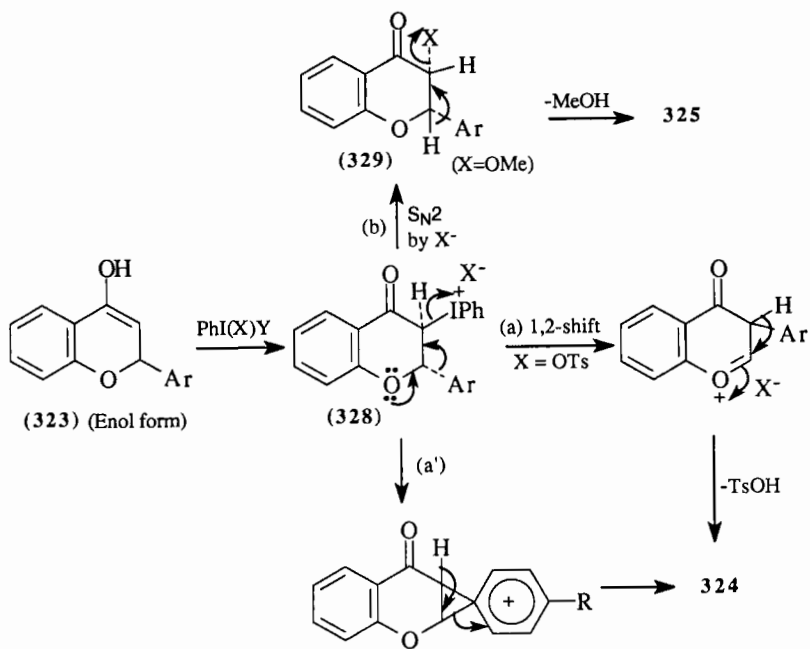


SCHEME 83

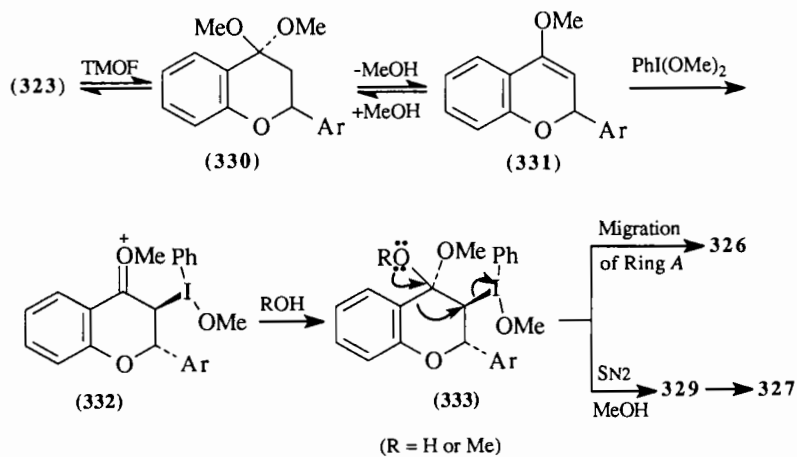
groups interferes these transformations. Another limitation of this approach is that the methoxyl group attached to the *ortho* position of ring *B* of flavanone causes problems.

The possible pathways for the transformations **323** → **324** and **323** → **325** are outlined in Scheme 84. The first step that is common to these reactions involves the electrophilic attack of the I(III) species on the enol form of **323** at the face of the molecule *anti* to the C(2)-aryl ring to provide intermediate **328**. Routes (a) and (a') involving a 1,2-aryl shift lead to isoflavones **324**. Route (b), involving S<sub>N</sub>2 attack of X<sup>-</sup>/XH at the C(3)-position of intermediate **328**, leads to **325** via **329**. The nucleophilicity of X<sup>-</sup>/XH plays a deciding role in affecting the course of the reaction.

The use of TMOF as a solvent provides strong acetalizing conditions (**323** → **330**). This allows the generation of enol ether **331**, which on electrophilic attack of hypervalent iodine species [PhI(OMe)<sub>2</sub>] (83IC1563) gives intermediate **332**. Nucleophilic attack of the solvent at the C(4)-position of **332**, followed by migration of ring *A*, results in the formation of **326**. The minor product **327** is resulted by a S<sub>N</sub>2 attack of methanol at the C(3)-position of **333** (Scheme 85).



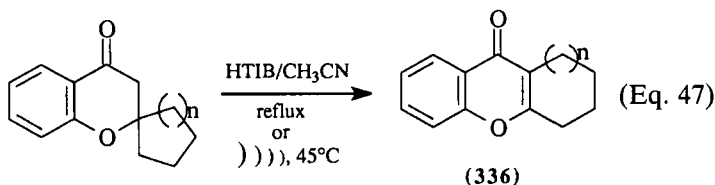
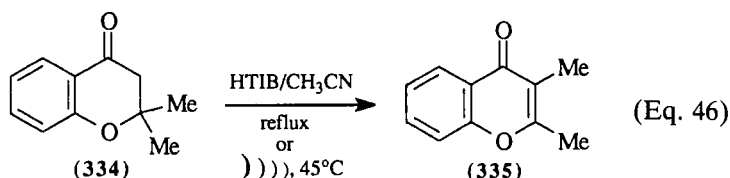
SCHEME 84



SCHEME 85

## H. REARRANGEMENT OF 2,2-DIALKYLCHROMANONES TO CHROMONES AND TETRAHYDROXANTHONES

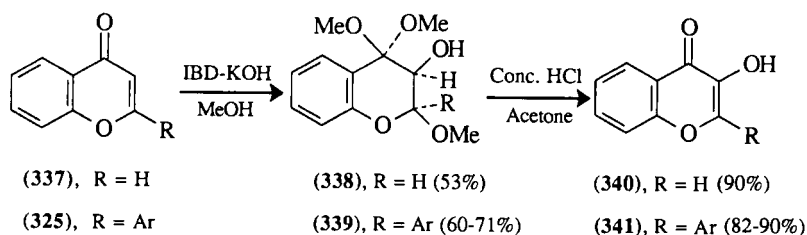
A rearrangement process analogous to that involved in conversion **323** to **324** (Scheme 83) occurs when several 2,2-dialkyl-substituted chromanones **334** are subjected to oxidation with HTIB. The reaction involving a 1,2-alkyl shift provides a convenient route for the synthesis of chromones **335** (Eq. 46), tetrahydroxanthones (**336**,  $n = 1$ ) and higher homologs (**336**,  $n = 2$ ) (Eq. 47). Both heat and ultrasonic conditions work well to effect this alkyl shift (94SC2637).



## I. C(3)-HYDROXYLATION OF CHROMONES AND FLAVONES TO CHROMONOLS AND FLAVONOLS

$\alpha,\beta$ -Unsaturated ketones such as chromone (**337**) and flavones **325**, which do not contain enolizable ketonic groups, also undergo oxidation with IBD-KOH/MeOH under standard conditions [85JHC583; 94IJC(B)272]. Interestingly, the reaction occurs regiospecifically and stereospecifically to give the corresponding  $\alpha$ -hydroxy- $\beta$ -methoxydimethylacetals **338** and **339**. Acid hydrolysis of **338** and **339** yields C(3)-hydroxylated chromone (**340**; chromonol) and flavones (**341**; flavonols) (Scheme 86).

The stereochemistry of **338** and **339** in each case results from initial conjugate addition of  $\text{MeO}^-$  at position 2 of the chromone ring. Ensuing attack of the formed enolate **342** upon  $\text{PhI(OMe)}_2$  occurs in an *anti* manner because of steric interaction. Sequential addition of  $\text{MeO}^-$  to the carbonyl group of **343** gives **344**, and intramolecular reductive elimination of  $\text{C}_6\text{H}_5\text{I}$  then occurs with inversion of configuration, **344**  $\rightarrow$  **345**. The reaction is

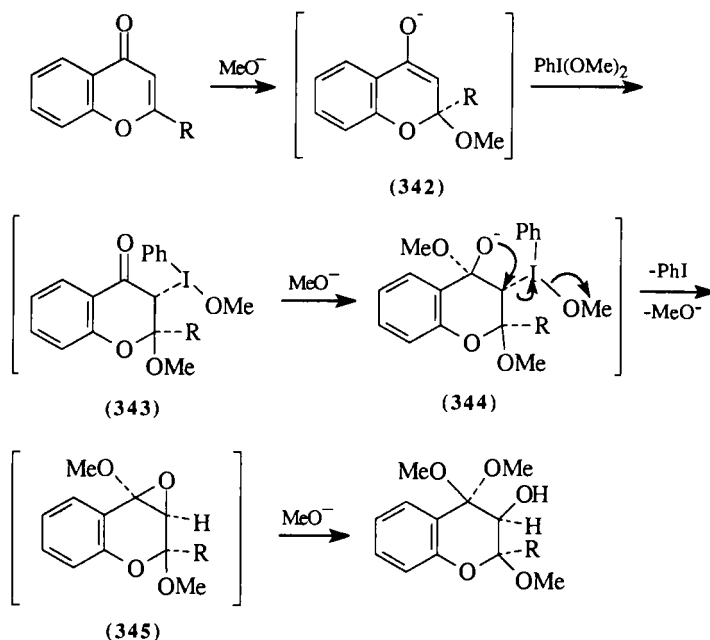


SCHEME 86

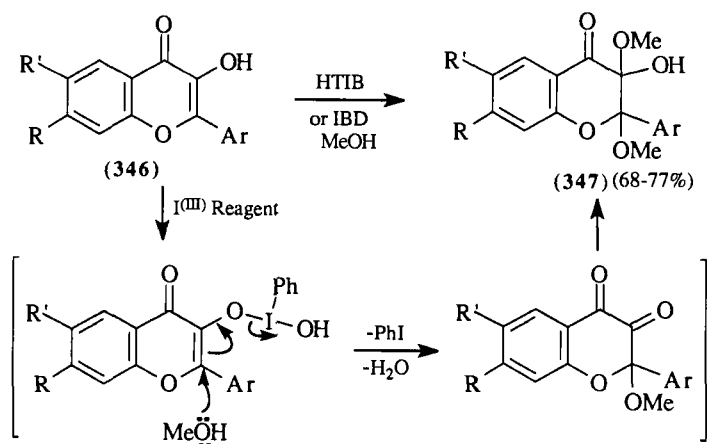
completed by a second addition of methoxide ion to the oxirane ring (Scheme 87).

### J. FLAVONOLS TO 2,3-DIMETHOXY-3-HYDROXYFLAVANONES

The oxidation of flavonols **346** with HTIB or IBD in methanol proceeds with the introduction of two methoxyl groups into the carbon-carbon double bond, and 2,3-dimethoxy-3-hydroxyflavanones **347** are obtained



SCHEME 87



SCHEME 88

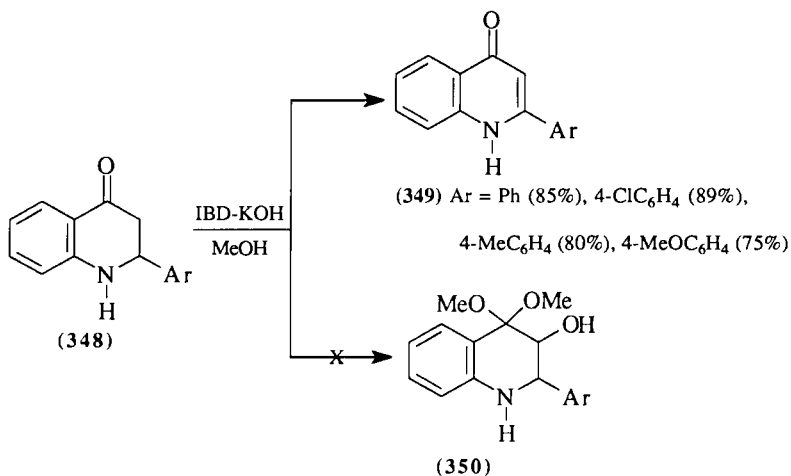
(86H1641). This transformation occurs according to a pathway analogous to oxidation of phenols (Scheme 88). An enolizable ketonic group such as propionyl present at position 6 of the flavonols (346,  $R' = \text{COCH}_2\text{CH}_3$ ) remains intact in this oxidation process (92SC893).

#### K. 1,2,3,4-Tetrahydro-4-quinolones to 4-quinolones

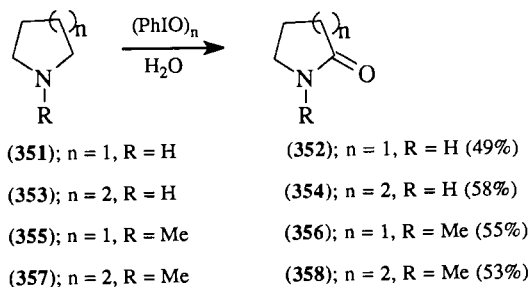
2-Aryl-1,2,3,4-tetrahydro-4-quinolones **348** can be dehydrogenated to the corresponding 4-quinolones **349** by using IBD-KOH/MeOH (94SC2167) (Scheme 89). Surprisingly, the expected product  $\alpha$ -hydroxydimethylacetal **350** is not obtained.

#### L. CYCLIC AMINES TO LACTAMS

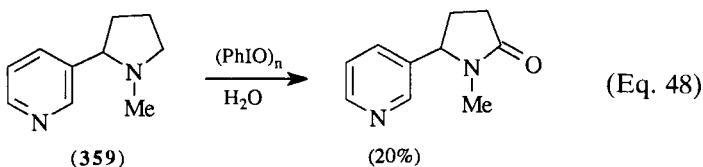
Oxidation of cyclic secondary amines such as pyrrolidine (**351**) and piperidine (**353**) with iodosobenzene in water leads to lactams **352** and **354**, respectively (88TL6913, 88TL6917) (Scheme 90). Similar oxidation of 2-piperidinecarboxylic acid and 2-pyrrolidinecarboxylic acid is accompanied by decarboxylation. Cyclic tertiary amines **355**, **357**, and **359** (Eq. 48) are likewise oxidized to the corresponding lactams. Other examples include phencyclidine (**360**) to *N*-(1-phenylcyclohexyl)piperidone (**361**), *N*-(cyanocyclohexyl)piperidine (**362**) to *N*-(1-cyanocyclohexyl)piperidone (**363**) (Scheme 91), and 1,2,3,4-tetrahydroisoquinoline to 1,2,3,4-tetrahydroisoquinolinone (Eq. 49).



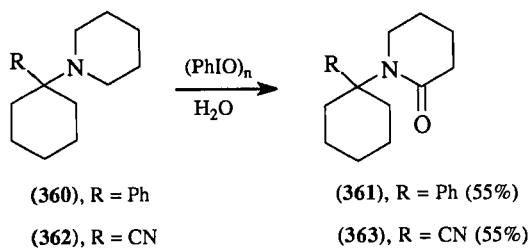
SCHEME 89



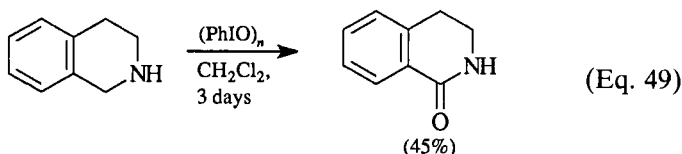
SCHEME 90



The lactam formation from the oxidation of cyclic amines (**353**, for example) probably proceeds via intermediate **364**. The nitrogen–iodine bond dissociates to give imine **365**, which reacts again with a second equivalent of iodosobenzene to give another intermediate **366**. Finally, **366** on reductive



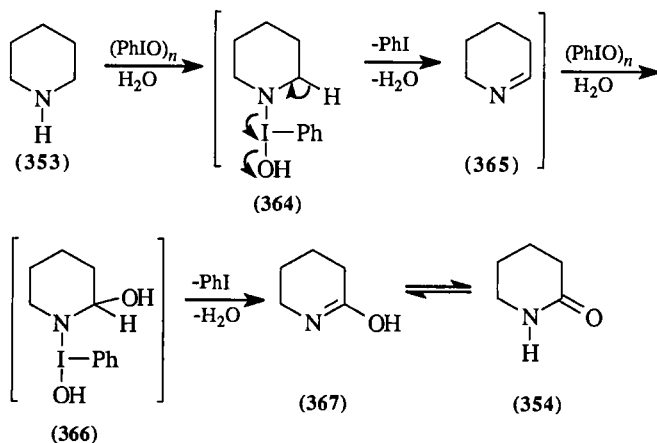
SCHEME 91



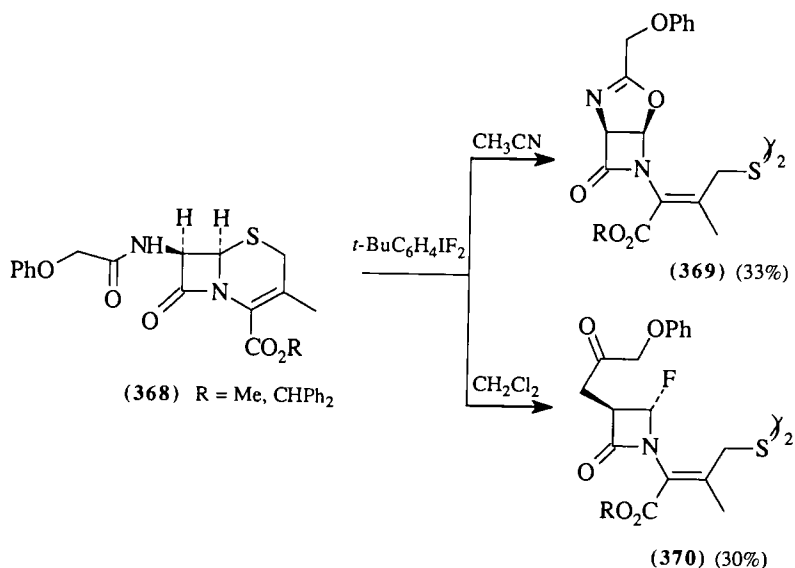
elimination of iodobenzene affords **367**, which tautomerizes to **354** (Scheme 92).

### M. CEPHALOSPORIN V TO OXAZOLINE DISULFIDES

Oxidation of esters of cephalosporin V (**368**) with 4-*tert*-butyl(difluoriodo)benzene in  $CH_3CN$  leads to the formation of oxazoline disulfides **369**. This is an example where cyclization occurring by intramolecular participa-

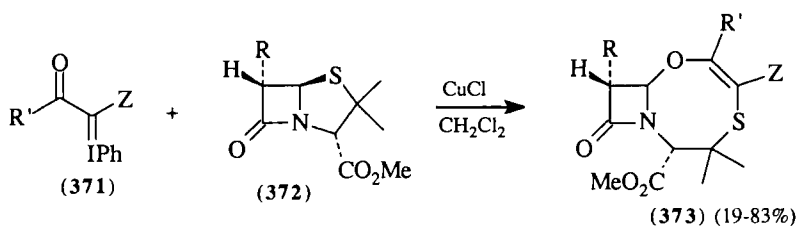


SCHEME 92



SCHEME 93

tion of an oxygen of amido group is accompanied by ring opening. The reaction is solvent dependent as the major product in dichloromethane is fluorazetidine **(370)** [71JCS(C)3540; 89JCS(CC)1348] (Scheme 93).



R	R'	Z
H	Me	COPh
H	Ph	COPh
H	Me	COMe
H	Me	CO <sub>2</sub> Et
H	Me	CO <sub>2</sub> <i>t</i> -Bu
	Me	COPh
	Ph	COPh

SCHEME 94



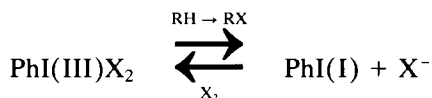
## N. RING EXPANSION OF PENAMS

Copper(I)-catalyzed reaction of stable iodonium ylides **371** derived from noncyclic  $\beta$ -keto esters and  $\beta$ -diketones with penams (**372**) provides the corresponding ring-expanded 1-aza-7-oxa-4-thiabicyclo[6.2.0]dec-5-en-10-ones (**373**) (90SL153) (Scheme 94). A more recent example of iodonium ylide based reaction involving intramolecular carbene nitrogen-hydrogen insertion includes an efficient synthesis of 1- $\beta$ -methylcarbapenes (95TL8043).

## IV. Conclusion

From a preparative viewpoint, use of organohypervalent iodine reagents and methods should definitely be considered in designing a given heterocyclic synthesis. This is true of the construction of a nucleus, as well as in the conversion of heterocycles to their functionalized derivatives. Many of the syntheses presented in the review are optimally carried out using organohypervalent iodine methodology. Particularly noteworthy are spirocyclization of substituted phenols, one-pot formation of tosylates followed by intramolecular heteroatom cyclization, and the wide range of heteroaromatic and heteroalicyclic compounds accessible via this methodology.

Operationally, the relevant reagents are easy to prepare, safe, and economical. The by-product, PhI, is easy to separate and, in principle, could be reoxidized. Furthermore, most of the reactions described are potentially scalable to multikilogram levels. A next step in this methodology would be catalytic regeneration of the I(III) reagent, that is,



but this has not as yet been accomplished. This review represents a first step in calling attention to this methodology, and the authors believe that use of organohypervalent iodine methods will assume a very important role in heterocyclic synthesis.

## ACKNOWLEDGMENTS

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# Chemistry of Pyrido[1,2-*b*][1,2]oxazines, Pyrido[1,2-*b*][1,2]thiazines, Pyrido[1,2-*b*]pyridazines, and Their Benzologs: Part I

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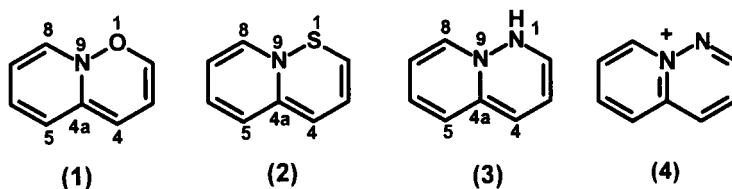
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## I. Introduction

The chemistry of the pyrido[1,2-*b*][1,2] oxazines (**1**), pyrido[1,2-*b*][1,2]thiazines (**2**), pyrido[1,2-*b*]pyridazines (**3**) (Scheme 1) and their benzologs (**5–13**) (Schemes 2 and 3) has not previously been reviewed. Only one publication on pyrido[1,2-*b*][1,2]oxazines is mentioned in the early review of Mosby in 1961 [61HC(15)1211], and pyrido[1,2-*b*]pyridazinium (**4**) is discussed in *Comprehensive Heterocyclic Chemistry* [84CHEC(2)572].

In preparing this article, the primary chemical literature through July of 1996 was surveyed. *Chemical Abstracts'* Subject and Chemical Substance Indexes through and including Volume 124 were searched. Throughout this article, the name and numbering style favored by *Chemical Abstracts* is used, and this style is indicated on Schemes 1–3.

Perhydro derivatives of pyrido[1,2-*b*][1,2]oxazines are frequently applied in the total synthesis of various alkaloids to control the stereochemistry, and 4-(substituted amino)-5-fluoro-7-oxo derivatives of 3,7-dihydro-2*H*-pyrido[3,2,1-*ij*][2,1]benzoxazine- and 1,2,3,7-tetrahydropyrido[3,2,1-*ij*]cinoline-8-carboxylic acids are considered as a subfamily of the third generation of antibacterial quinolones.



SCHEME 1

In the following sections, physicochemical properties, syntheses, reactions, and the utilization of the most important compounds are discussed. Within the individual sections, the pyrido[1,2-*b*][1,2]oxazines and their benzologs, followed by pyrido[1,2-*b*][1,2]thiazines, pyrido[1,2-*b*]pyridazines, and their benzologs, are dealt with.

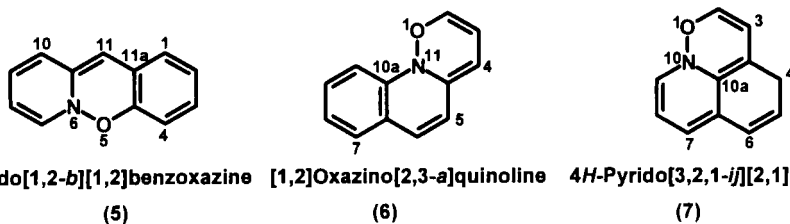
## II. Structure

### A. PYRIDO[1,2-*b*][1,2]OXAZINES AND THEIR BENZO DERIVATIVES

#### 1. NMR Studies

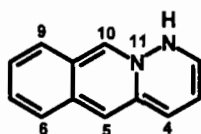
$^1\text{H}$  and  $^{13}\text{C}$  NMR conformational studies revealed that *cis*-2,4*a*,8-*H*-2-butyl-8-propylperhydropyrido[1,2-*b*][1,2]oxazine (**14**,  $\text{R} = n\text{Bu}$ ,  $\text{R}^1 = \text{H}$ ) exists in pyridine- $d_5$  at 27.5°C in an equilibrium involving nearly equal populations of *trans*- and *cis*-fused forms due to nitrogen inversion (85JA5534; 89JOC4088). The inversion barrier ( $\Delta G^\ddagger$ ) was estimated to be about 8.0 kcal mol $^{-1}$ . The C(2) proton signals converged to a single resonance at  $\delta$  3.88 ppm at 100°C. *r*-2,*c*-4*a*,*t*-5,*c*-8-*H*-2-Ethyl-5-benzyloxy-8-propylperhydropyrido[1,2-*b*][1,2]oxazine (**14**,  $\text{R} = \text{Et}$ ,  $\text{R}^1 = \text{PhCH}_2\text{O}$ ) exists in pyridine- $d_5$  as a 1:2 mixture of *trans*- and *cis*-fused conformers [96JCS(P1)1113]. NOE experiments indicated that *r*-4*a*,*t*-5,*c*-8-*H*-8-substi-

#### Benzo Derivatives of Pyrido[1,2-*b*][1,2]oxazine

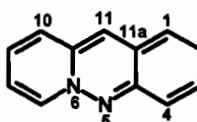


Pyrido[1,2-*b*][1,2]benzoxazine (5)    [1,2]Oxazino[2,3-*a*]quinoline (6)    4*H*-Pyrido[3,2,1-*i*][2,1]benzoxazine (7)

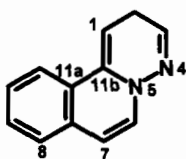
SCHEME 2

Benzo Derivatives of Pyrido[2,1-*b*]pyridazine

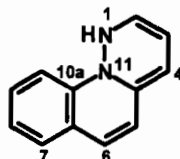
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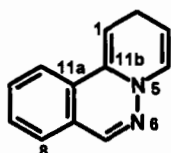
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1*H*-Pyridazino[1,6-*b*]isoquinoline2*H*-Pyrido[1,2-*b*]cinnoline

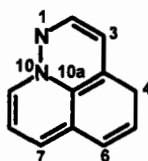
(10)



(11)

2*H*-Pyridazino[6,1-*a*]isoquinoline1*H*-Pyridazino[1,6-*a*]quinoline

(12)

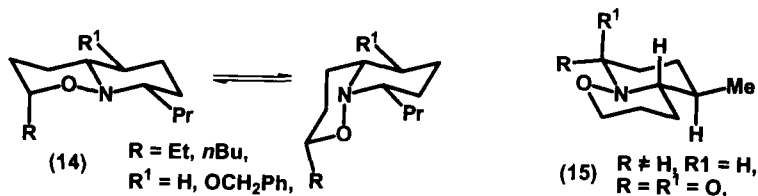


(13)

2*H*-Pyrido[2,1-*a*]phthalazine1*H*,4*H*-Pyrido[3,2,1-*h*]cinnoline

SCHEME 3

tuted 5-methyl- and *trans*-4*a*,5-*H*-8-oxo-5-methylperhydropyrido[1,2-*b*]-[1,2]oxazines (**15**) adopt a *trans*-fused all-chair conformation with an equatorial methyl group [91JCS(CC)1237; 92JOC2876].



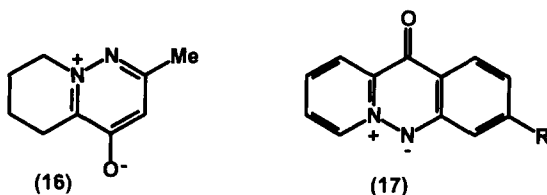
## B. PYRIDO[1,2-*b*][1,2]THIAZINES

No pyrido[1,2-*b*][1,2]thiazine derivative has been the subject of theoretical or experimental structural studies.

## C. PYRIDO[1,2-*b*]PYRIDAZINES AND THEIR BENZO DERIVATIVES

### 1. Thermodynamic Aspects

The  $pK_a$  values of perhydropyrido[1,2-*b*]pyridazine and its 2-oxo derivative were found to be  $2.80 \pm 0.04$  and  $7.32 \pm 0.03$ , respectively (72KGS220), whereas that of *anhydro* 4-hydroxy-2-methyl-5,6,7,8-tetrahydropyrido[1,2-*b*]pyridazinium hydroxide (16) was determined by spectrophotometry to be 2.77 (71CPB159). UV spectroscopic measurements in sulfuric acid gave a  $pK_a$  value of  $-0.25$  for pyrido[1,2-*b*]cinnoline derivative (17, R = H) (74JHC125).



The lone-pair peak separation of 1.04 eV, measured by means of photoelectron spectroscopy, was indicative of the presence of the *trans*-fused conformation with an axial methyl group for 1-methylperhydropyrido[1,2-*b*]pyridazine (18) (79JA1874). Ionization potentials and the oxidation potential of 1-methylperhydropyrido[1,2-*b*]pyridazine have been determined (79IJ45, 79JA1874; 84JOC1891).





### 5. $^1\text{H}$ NMR Spectroscopy

Hexahydro-8*H*-pyrido[1,2-*b*]pyridazin-8-ones (**23**) are *trans*-fused bicycles. The  $^1\text{H}$  NMR signal for the bridgehead hydrogen appears as triplet in the range of 3.3–3.5 ppm ( $J$  11–12 Hz) and display further splitting [87JCS(P1)2511].

The relatively low chemical shift (1.30 ppm) of the 5-methyl group in hexahydro-4*aH*-pyridazino[1,6-*b*]isoquinoline points to the presence of a *trans*-fused conformer **22** with an axial 5-methyl group (73JHC999).

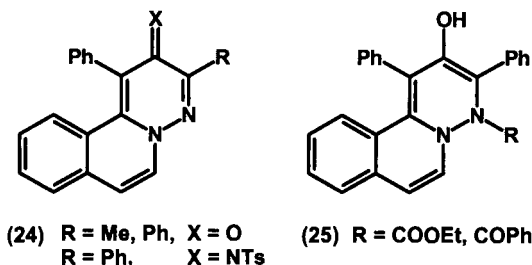
### 6. $^{13}\text{C}$ NMR Spectroscopy

Of the six possible conformers containing chair rings, two *trans*-fused conformers **18** and **19**, with a slight excess of **18**, could be identified as major conformers, with one *cis*-fused conformer as a minor constituent in the  $^{13}\text{C}$  NMR spectrum of 1-methylperhydropyrido[1,2-*b*]pyridazine in acetone- $d_6$  in the temperature range  $-75$  to  $-89^\circ\text{C}$  (78JA4012). The low intensity of the signal of the *cis*-fused conformer did not allow determination of the exact structure of this component. The results of low-temperature cyclic voltammetry experiments supported the NMR findings.

### 7. Mass Spectroscopy

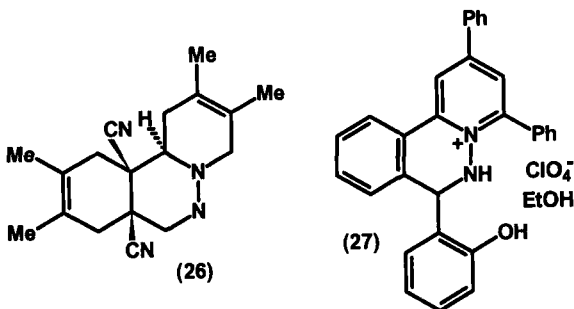
The fragmentation pattern of 1,5-dimethyl-7-methoxy-1,2,3,4,5,10-hexahydro-4*aH*-pyridazino[1,6-*b*]isoquinoline (**22**) has been studied (73JHC999). The base peak at  $m/e$  148 might be derived through the retro Diels–Alder fission of the molecular ion. The 7-hydroxy derivative gives the same fragmentation pattern.

The mass spectral fragmentations of pyridazino[6,1-*a*]isoquinolines **24** and **25** have also been investigated (85OMS483).



### 8. X-Ray Investigations

The structure of a pyrido[1,2-*b*]cinnoline (**17**, R = Br) (74JHC125), a pyrido[2,1-*a*]phthalazine (**26**) (94T9189), and 2,4-diphenyl-7-*o*-hydroxyphenyl-5,6-dihydropyrido[2,1-*a*]phthalazinium perchlorate (**27**) (95IZV296) have been established by X-ray crystallographic analysis.



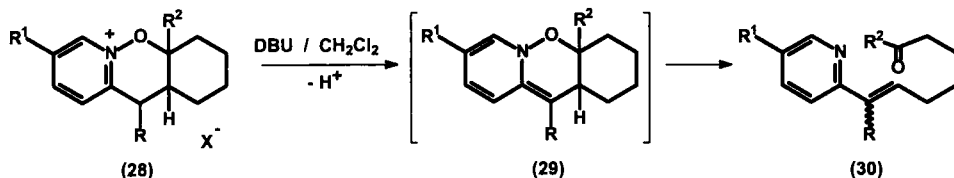
## III. Reactivity

### A. PYRIDO[1,2-*b*][1,2]OXAZINES AND THEIR BENZO DERIVATIVES

#### 1. Ring Opening

Reductive N—O bond cleavage of perhydropyrido[1,2-*b*][1,2]oxazines with Zn dust in 60–80% aqueous acetic acid [85JA5534; 86TL5513; 89JOC4088; 91JCS(CC)1237, 91TL4325; 92JOC2876; 96JCS(P1)1113], or by hydrogenation over 5% Pd/C (89JOC4088) furnished the corresponding 2-(3-hydroxypropyl)piperidines, and that of 2,4*a*,5,6,7,8-hexahydropyrido[1,2-*a*][1,2]oxazines (89JOC4088) and their 8-oxo derivatives (93JOC6083; 94JOC1358) with Zn in aqueous acetic acid or with sodium amalgam in the presence of Na<sub>2</sub>HPO<sub>4</sub>, respectively, gave 2-[(*Z*)-3-hydroxy-1-propenyl]piperidines and their 6-oxo derivatives. 2-(3-Hydroxypropyl)piperidine hydrobromide and 2-vinylpyridine were obtained when 2,3-dihydro-4*H*-pyrido[1,2-*b*][1,2]oxazonium hydrobromide was hydrogenated over Adams catalyst or treated with an aqueous alkaline solution, respectively (58JA2217).

Treatment of pyrido[1,2-*b*][1,2]benzoxazinium salts (**28**) with DBU gave ring-opened products **30** as *E/Z* mixtures (81AGE481). In the first step, deprotonation occurred, and **29** then underwent cycloreversion.

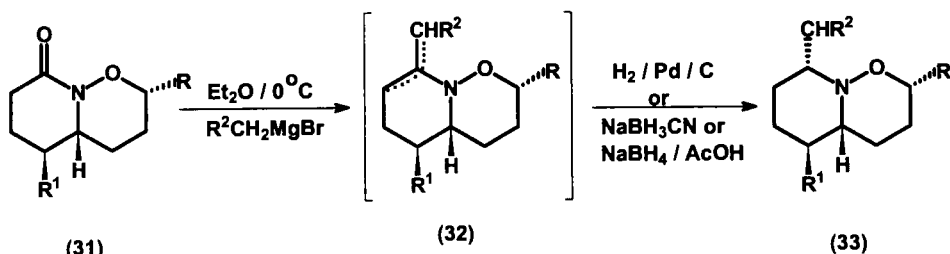


## 2. Reduction

The 3,4-double bond of 2,4*a*,5,6,7,8-hexahydropyrido[1,2-*b*][1,2]oxazin-8-ones was hydrogenated over Pd/C to yield perhydropyrido[1,2-*b*][1,2]oxazin-8-ones [85JA5534; 89JOC4088; 91JCS(CC)1237, 91TL4325; 92JOC2876; 94TL9213; 96JCS(P1)1113]. The 8-(4-heptynyl) side chain of a perhydropyrido[1,2-*b*][1,2]oxazine was reduced to a 8-[(*Z*)-heptenyl] group over the Lindlar catalyst [91JCS(CC)1237; 92JOC2876].

## 3. Reactivity of Rings

A Grignard reaction of the 8-oxo group of **31** with an alkylmagnesium bromide gave a mixture of unstable endocyclic and exocyclic enamines **32**, which were immediately subjected to reduction with hydrogen over 5% Pd/C in methanol (86TL5513; 89JOC4088), with sodium cyanoborohydride in acidified methanol [85JA5534; 89JOC4088; 96JCS(P1)1113] or with sodium borohydride in acetic acid [91JCS(CC)1237; 92JOC2876] to give stereospecifically a single stereoisomer **33**. Similar reactions were carried out with 3-lithiofuran instead of alkylmagnesium bromide (91TL4325).

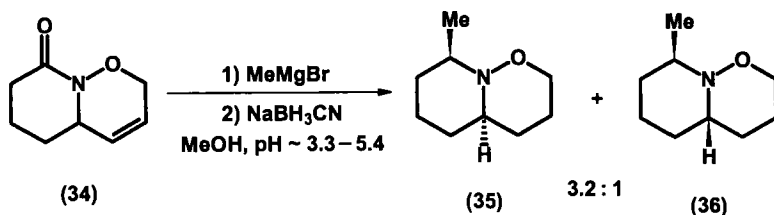


$R = H, Et, Bu; R^1 = H, Me, OCH_2Ph;$

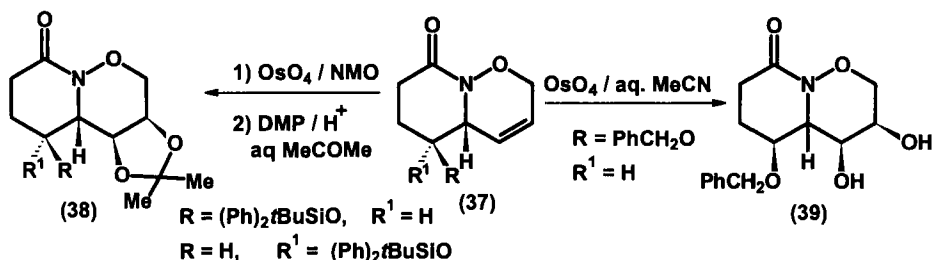
$R^2 = H, Et, 3\text{-furyl}, -CH_2CH_2C\equiv CSiMe_3, -CH_2CH_2C\equiv CEt, -CH_2CH_2CH=CH_2$

When a similar reaction sequence was carried out with 2,4*a*,5,6,7,8-hexahydropyrido[1,2-*b*][1,2]oxazin-8-one (**34**), a 3.2:1 mixture of the 8-

methyl derivatives of *cis*-4*a*,8-H and *trans*-4*a*,8-H-2,4*a*,5,6,7,8-hexahydro-pyrido[1,2-*b*][1,2]oxazines (**35** and **36**) was obtained (89JOC4088).



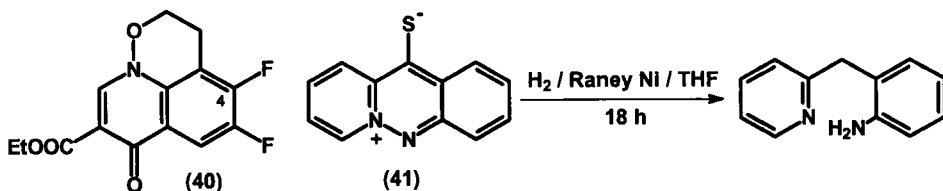
Acetonides **38** were prepared by the reaction of **37** and *N*-methylmorpholine oxide (NMO) in the presence of a catalytic amount of OsO<sub>4</sub>, followed by treatment with 2,2-dimethoxypropane in the presence of Dowex (H<sup>+</sup>) resin (93JOC6083). In aqueous acetonitrile, the (3*S*,4*R*)-3,4-dihydroxy derivative **39** was the product (94JOC1358).



The 4-fluoro atom of 4,5-difluoro-7-oxo-2,3-dihydro-7*H*-pyrido[3,2-*i*]-[2,1]benzoxazine-8-carboxylate (**40**) was regioselectively substituted by cyclic amines in DMSO at 100–110°C [92JAP(K)92/208288, 92JAP(K)92/210656].

#### 4. Reactivity of Substituents Attached to Ring Carbon Atoms

The hydroxy groups of **39** was acylated with acetic anhydride in pyridine (94JOC1358). The ester group of 4,5-difluoro-7-oxo-2,3-dihydro-7*H*-pyrido[3,2-*i*]-[2,1]benzoxazine-8-carboxylate (**40**) was hydrolyzed under acidic conditions [92JAP(K)92/208288, 92JAP(K)92/210656].



B. PYRIDO[1,2-*b*][1,2]THIAZINES1. *Reactivity of Rings*

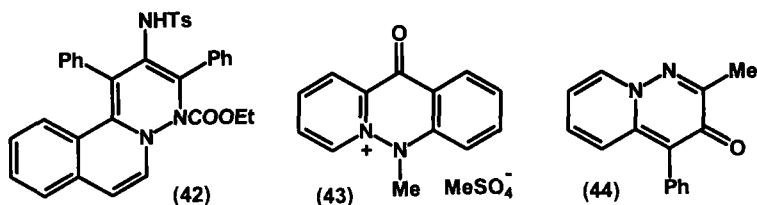
The 2-ethyl derivative was obtained in 18% yield when perhydropyrido[1,2-*b*][1,2]thiazine-1,1-dioxide was treated with Na in boiling toluene, and then with ethyl iodide at 60–70°C (62AP615). The stereochemistry of the product was not investigated.

C. PYRIDO[1,2-*b*]PYRIDAZINES AND THEIR BENZO DERIVATIVES1. *Ring Opening*

When the hydrochloride salt of 2,3,4,4*a*,5,6-hexahydro-1*H*-pyridazino[1,6-*a*]quinoline was subjected to catalytic hydrogenation in ethanol over PtO<sub>2</sub>, 3-[2-(1,2,3,4-tetrahydroquinolyl)]propylamine was obtained (66YZ608). Catalytic reduction of perhydropyrido[1,2-*b*]pyridazine over a skeletal nickel catalyst in ethanol at 30 atm gave ring-opened 2-(3-aminopropyl)piperidine (66KGS91).

Catalytic reduction of 11-mercaptopyrido[1,2-*b*]cinnolin-6-ium hydroxide inner salt (**41**) over Raney Ni yielded 2-(2-aminobenzyl)pyridine (74JHC125). When a 36-h reaction period was applied in the hydrolysis of **42**, 1-benzylisoquinoline was obtained (83JOC1084).

Ring-opened products were obtained from pyrido[1,2-*b*]cinnolin-6-ium hydroxide inner salt (**17**, R = H) by oxidation with 3-chloroperoxybenzoic acid, or by reduction with Zn in acetic acid, and from the 5-methyl derivative **43** by reduction with Zn in acetic acid (74JHC125).

2. *Reduction, Hydrogenation, Dehydrogenation*

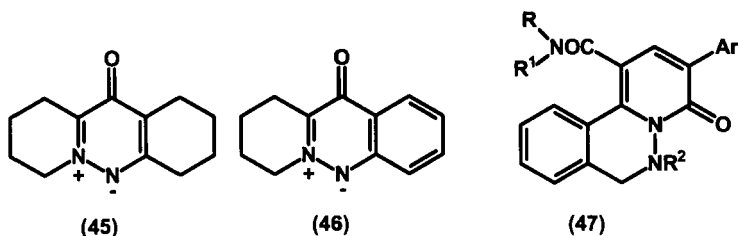
Perhydropyrido[1,2-*b*]pyridazine was prepared from perhydropyrido[1,2-*b*]pyridazin-2-one by reduction with LAH (65MI1, 65URP170506; 66KGS91; 78JA4012), and from 4,4*a*,5,6,7,8-hexahydro-3*H*-pyrido[1,2-*b*]pyridazine by catalytic reduction over PtO<sub>2</sub> in acetic acid (68YZ216). Re-

duction of 3,4,5,6-tetrahydro-4*aH*-pyridazino[1,6-*a*]quinoline over  $\text{PtO}_2$  in acetic acid gave 2,3,4*a*,4,5,6-hexahydro-1*H*-pyridazino[1,6-*a*]quinoline (66YZ608).

Reduction of 2-methyl-4-phenyl-3*H*-pyrido[1,2-*b*]pyridazin-3-one (**44**) with  $\text{NaBH}_4$  in ethanol afforded the 5,6,7,8-tetrahydro derivative [76JCS(CC)275; 78JOC2892].

Reduction of 1-acetyl-, 1-benzyl-, and 1-cyanomethylperhydropyrido[1,2-*b*]pyridazines with LAH afforded 1-ethyl-, 1-benzyl-, and 1-(2-aminoethyl) derivatives, respectively (65MI1; 66KGS91).

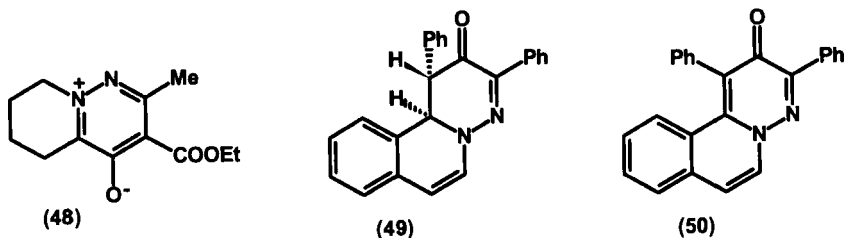
Reduction of **17** ( $\text{R} = \text{H}$ ) over  $\text{Pd/C}$  in 0.2 *N* hydrochloric acid (75JOC2201) or over Raney Ni in tetrahydrofuran (74JHC125) gave the 1,2,3,4,7,8,9,10-octahydro derivative **45**. Hydrogenation over  $\text{Pd/C}$  in THF afforded a mixture of **45** and **46** (74JHC125).



Reduction of 3-aryl-4-oxo-4*H*-pyrido[2,1-*a*]phthalazine-1-carboxamides with sodium cyanoborohydride in acidified methanol or lithium borohydride in tetrahydrofuran afforded 6,7-dihydro derivatives **47** ( $\text{R}^2 = \text{H}$ ) (88EUP294599).

Dehydrogenation of ethyl 2-methyl-4-hydroxy-5,6,7,8-tetrahydro-4*aH*-pyrido[1,2-*b*]pyridazine-3-carboxylate with mercury(II) acetate in ethanol at 45–50°C or over  $\text{PtO}_2$  in boiling ethanol afforded *anhydro* 3-ethoxycarbonyl-2-methyl-4-hydroxy-5,6,7,8-tetrahydropyrido[1,2-*b*]pyridazinium hydroxide (**48**) (71CPB159). The last compound could be reduced to the starting tetrahydropyrido[1,2-*b*]pyridazine over  $\text{PtO}_2$  in ethanol under hydrogen.

When 1,11*b*-dihydropyridazino[6,1-*a*]isoquinoline (**49**) was heated in benzene, dehydrogenated derivative **50** was obtained (83JOC1084).

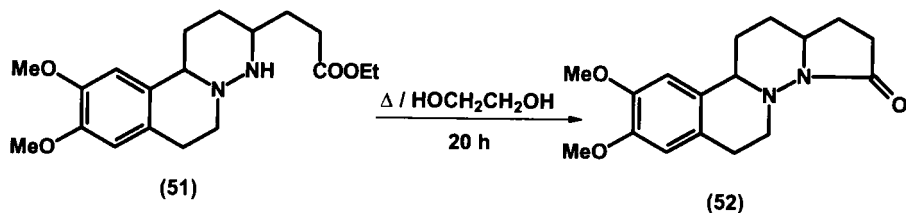


### 3. Reactivity of Ring Nitrogen Atoms

Perhydropyrido[1,2-*b*]pyridazine and its 2-oxo derivative were alkylated in position 1 by reductive methylation with sodium cyanoborohydride and formaldehyde (78JA4012), and acylated with acid anhydride and acid chlorides (65MI1; 66KGS91). The 1-benzoyl derivative was prepared from 2,3,4,4a,5,6-hexahydro-1*H*-pyridazino[1,6-*a*]quinoline (66YZ608). The 1-(*N*-phenylcarbamoyl), 1-cyanomethyl, and 1-(*N*-naphthylthiocarbamoyl) derivatives of perhydropyrido[1,2-*b*]pyridazine were prepared from perhydropyrido[1,2-*b*]pyridazine with phenyl isocyanate (65MI1; 66KGS91), with sodium cyanide and hydroxymethyl sulfonate (66KGS91), and with 1-naphthyl isothiocyanate (68YZ216), respectively. 4-(6-Ethyl- and 6-benzyl-6,7-dihydro-3-aryl-4-oxo-4*H*-pyrido[2,1-*a*]phthalazine-1-carbonyl)morpholines (**47**,  $RR^1N$  = morpholino,  $R^2$  = Et,  $PhCH_2$ ) were prepared from the 6-unsubstituted derivatives **47** ( $RR^1N$  = morpholino,  $R^2$  = H) with ethyl iodide and benzyl chloride, respectively (88EUP294599).

The 5-methyl derivative **43** was obtained from pyrido[1,2-*b*]cinnolin-6-ium hydroxide inner salt **17** ( $R$  = H) with dimethyl sulfate (74JHC125). Protonation of **17** ( $R$  = H) occurred on the 5-nitrogen and not the oxygen, but its 1,2,3,4,7,8,9-octahydro derivative **45** was protonated on the oxygen to produce the 11-hydroxy salt.

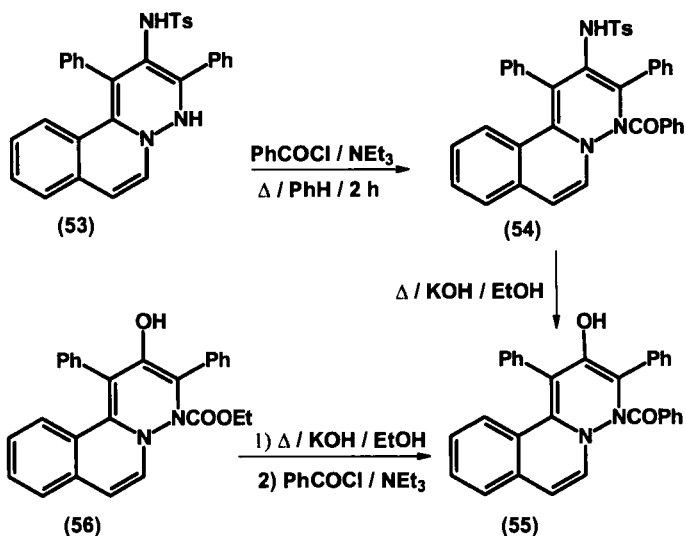
Heating 3-(hexahydro-1*H*-pyrido[2,1-*a*]phthalazin-3-yl)propionate (**51**) in gently boiling ethylene glycol afforded the diazasteroid **52** (75CPB3056).



Boiling an ethanolic solution of 4*H*-pyridazino[6,1-*a*]isoquinoline (**42**) in the presence of KOH for 6 h gave the 4-unsubstituted derivative **53**, which was *N*-acylated with benzoyl chloride (83JOC1084). Heating the *N*-benzoyl derivative **54** in boiling ethanol in the presence of KOH for 36 h afforded the 2-hydroxy derivative **55**, which was also prepared from **56** by basic hydrolysis and subsequent acylation with benzoyl chloride. A decarboxylation-oxidation product **50** was also isolated from the reaction mixture.

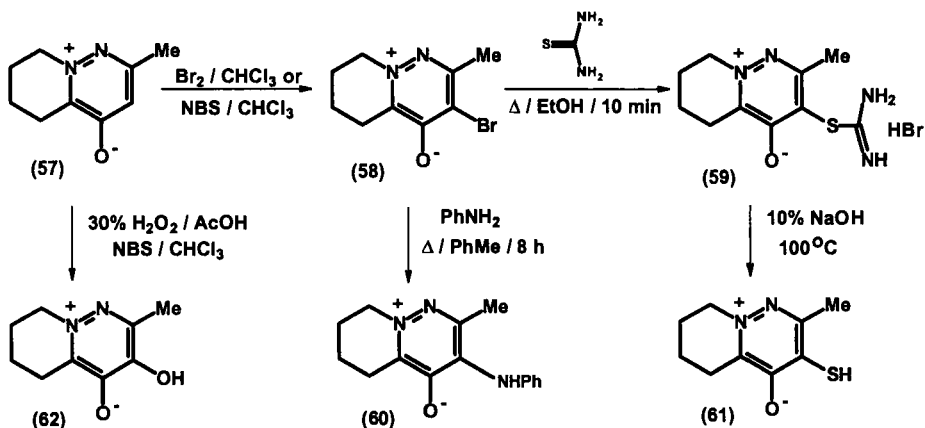
1-Unsubstituted 7-oxo-1,2,3,7-tetrahydropyrido[3,2,1-*ij*]cinnoline-8-carboxylates were *N*-alkylated with dialkyl sulfates, and they were also *N*-acylated with acetic anhydride in acetic acid to give the 1-substituted derivatives (92EUP470578). The 1-hydroxymethyl derivatives were prepared from the 1-unsubstituted compound with formalin in acetic acid.





#### 4. Reactivity of Ring Carbon Atoms

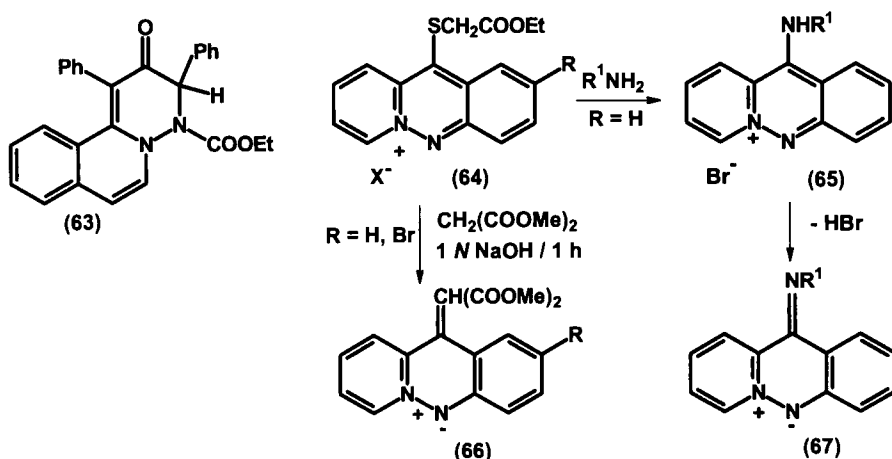
Position 3 of *anhydro* 2-methyl-4-hydroxy-5,6,7,8-tetrahydropyrido[1,2-*b*]pyridazinium hydroxide (**57**) was subjected to both electrophilic and nucleophilic substitution to give **58–61** (71CPB159). Treatment of **57** with  $\text{H}_2\text{O}_2$  gave the 3-hydroxy derivative **62**.



The heating of pyridazino[6,1-*a*]isoquinoline **63** in an ethanolic potassium hydroxide solution afforded a mixture of pyridazino[6,1-*a*]isoquinolines **50**, **56**, and its 4-deethoxycarbonyl derivative (83JOC1084).

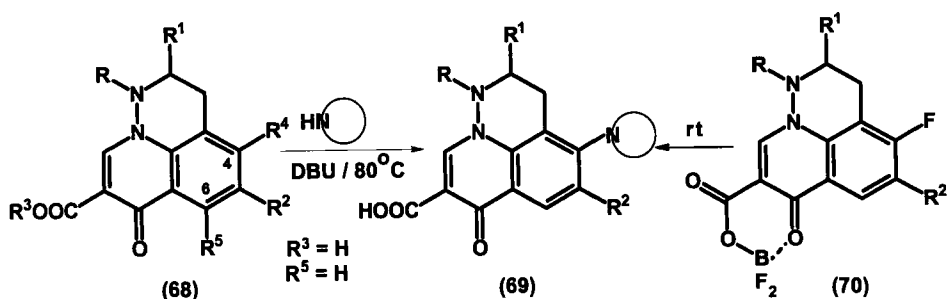
Nitration of pyrido[1,2-*b*]cinnolin-6-ium hydroxide inner salt **17** ( $R = H$ ) and its 2-acetamide derivative afforded its 2-nitro and 2-acetamido-3-nitro derivatives, respectively. The reaction of **17** ( $R = H$ ) with iodine monochloride afforded the 2-iodo derivative. The 2-cyano derivative was obtained from the 2-bromo derivative of **17** ( $R = H$ ) with  $\text{Cu(I)CN}$ . Treatment of **17** ( $R = H$ ) with  $\text{P}_4\text{S}_{10}$  afforded the 11-mercapto derivative **41** (74JHC125).

Substitution of the 11-ethoxycarbonylmethylthio group of **64** with anilines, 3-dimethylaminopropylamine, thiosemicarbazide, acetylhydrazine, and dimethyl malonate gave the corresponding 11-amine **65** and 11-bis(dimethoxycarbonyl)methylene derivatives **66** (74JHC125). Deprotonation of the 11-amines **65** gave the 11-imino derivatives **67**.



The fluoro atom in 4-fluoro-7-oxopyrido[3,2,1-*ij*]cinnoline-8-carboxylic acids or esters (**68**,  $R^4 = F$ ,  $R^5 = H$ ) was substituted with *N*-, *O*-, *S*-, and *C*-nucleophiles: for example, with cyclic amine in the presence of a base, with a primary or secondary alcohol in the presence of sodium hydride, with an alkyl mercaptan in the presence of a base, or with carbanions of alkyl cyanoacetates formed with sodium hydride [92EUP470578, 92MIP1; 93JAP(K)93/213951; 94JAP(K)94/228138]. Substitution of the fluoro atom in **68** ( $R^4 = F$ ,  $R^5 = H$ ) with an amine was usually carried out in a dipolar solvent at  $80^\circ\text{C}$  to give **69**, but it occurred at room temperature when a boron chelate **70**, containing a more reactive halogen at position 4, was applied (92EUP470578). The 6-fluoro atom in ethyl 4,5,6-trifluoro-1-methyl-7-oxo-2,3-dihydro-1*H*,7*H*-pyrido[3,2,1-*ij*]cinnoline-8-carboxylate (**68**,  $R = \text{Me}$ ,  $R^1 = H$ ,  $R^2 = R^4 = R^5 = F$ ,  $R^3 = \text{Et}$ ) was regioselectively substituted by benzylamine in toluene at  $80^\circ\text{C}$  (92EUP470578). 5-Fluoro-4-hydroxy-2,3-dihydro-1-methyl-7-oxo-1*H*,7*H*-pyrido[3,2,1-*ij*]cinnoline-8-carboxylic acid (**68**,  $R = \text{Me}$ ,  $R^1 = R^3 = R^5 = H$ ,  $R^2 = F$ ,  $R^4 = \text{OH}$ ) was

obtained from the 4,5-difluoro derivative by heating in 30% aqueous KOH and the 4-hydroxy group was reacted with alkyl or arylsulfonyl chlorides and trifluoromethanesulfonic anhydride. The 4-(3-oxo-1-cyclohexen-1-yl) derivative was prepared from methyl 5-fluoro-4-(trifluoromethanesulfonyloxy)-2,3-dihydro-1-methyl-7-oxo-1*H*,7*H*-pyrido[3,2,1-*ij*]cinnoline-8-carboxylate (**68**, R = Me, R<sup>1</sup> = R<sup>5</sup> = H, R<sup>2</sup> = F, R<sup>3</sup> = Me, R<sup>4</sup> = CF<sub>3</sub>SO<sub>2</sub>O) with 3-tributylstannyl-2-cyclohexen-1-one in the presence of LiCl in boiling THF for 3 days.



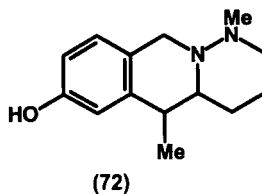
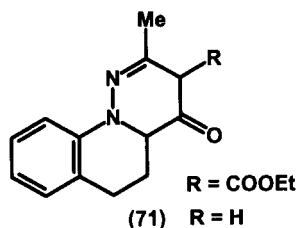
When ethyl 4,5,6-trifluoro-1-methyl-7-oxo-1,2,3,7-tetrahydropyr-ido[3,2,1-*ij*]-cinnoline-8-carboxylate (**68**, R = Me, R<sup>1</sup> = H, R<sup>2</sup> = R<sup>4</sup> = R<sup>5</sup> = F, R<sup>3</sup> = Et) was reacted with the sodium salt of bis(*tert*-butyl) malonate at room temperature, the 6-[bis(*tert*-butoxycarbonyl)methyl]derivative was obtained [93JAP(K)93/279364].

Methyl 5-fluoro-4-(trifluoromethylsulfonyloxy)-2,3-dihydro-1-methyl-7-oxo-1*H*,7*H*-pyrido[3,2,1-*ij*]cinnoline-8-carboxylate (**68**, R = Me, R<sup>1</sup> = R<sup>5</sup> = H, R<sup>2</sup> = F, R<sup>3</sup> = Me, R<sup>4</sup> = CF<sub>3</sub>SO<sub>2</sub>O) was reacted with 3-tributylstannyl-2-cyclohexen-1-one in the presence of lithium chloride and bis(triphenylphosphine)palladium(II) chloride in tetrahydrofuran for 3 days to give a 4-(3-oxo-1-cyclohexen-1-yl)derivative (92EUP470578).

## 5. Reactivity of Substituents Attached to Ring Carbon Atoms

The cyano group of 1-(cyanomethyl)perhydropyrido[1,2-*b*]pyridazine was reduced with LAH to yield the 1-(2-aminoethyl) derivative (66KGS91). The amino group was reacted with methyl isothiurea in boiling 50% aqueous ethanol to afford the 1-(2-guanidinoethyl) derivative (66KGS91).

2-Methyl-3,4,5,6-tetrahydro-4*aH*-pyridazino[1,6-*a*]quinolin-4-one (**71**, R = H) was obtained when ethyl 2-methyl-4-oxo-3,4,5,6-tetrahydro-4*aH*-pyridazino[1,6-*a*]quinoline-3-carboxylate (**71**, R = COOEt) was boiled in 40% aqueous ethanol for 30–45 h (66YZ613). The ester group of **48** could be hydrolyzed with 10% aqueous NaOH to give the carboxyl derivative, which

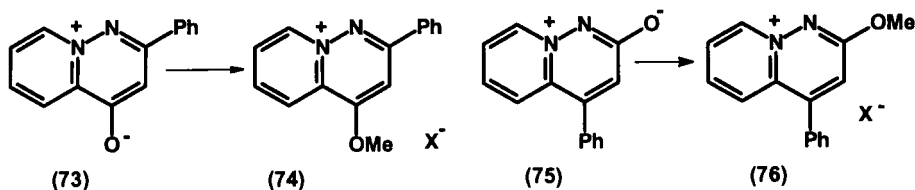


was decarboxylated in boiling 20% hydrochloric acid to yield *anhydro* (4-hydroxy-2-methyl-5,6,7,8-tetrahydropyrido[1,2-*b*]pyridazinium hydroxide (**57**) (71CPB159).

When the 3-thiourea derivative (**59**) was heated in boiling ethanol for 3 h, and then the evaporated reaction mixture was treated with 10% NaOH solution at 100°C for 20 min, *anhydro* 2-methyl-3-mercapto-4-hydroxy-5,6,7,8-tetrahydro[1,2-*b*]pyridazinium hydroxide (**61**) was obtained (71CPB159). The mercapto group was alkylated with benzyl bromide and was treated with HgCl<sub>2</sub> in boiling ethanol to yield the 3-chloromercurithio derivative. *Anhydro* 3,4-dihydroxy-2-methyl-5,6,7,8-tetrahydropyrido[1,2-*b*]pyridazinium hydroxide (**62**) was *O*-acylated with acetic anhydride, but the structure of the product was not elucidated (71CPB159).

7-Hydroxy-1,5-dimethyl-1,2,3,4,5,10-hexahydro-4*aH*-pyridazino[1,6-*b*]isoquinoline (**72**) was prepared from the 7-methoxy derivative **22** by heating in boiling acetic acid in the presence of 48% hydrogen bromide (73JHC999).

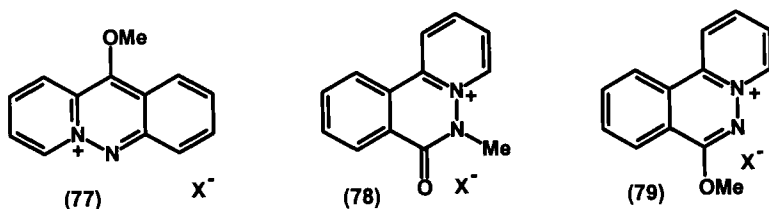
Deprotonation of 7-hydroxypyrido[2,1-*a*]phthalazinium perchlorate with NEt<sub>3</sub> in ethanol gave pyrido[2,1-*a*]phthalazinium-7-olate (**20**) (92CB929). 4-Hydroxy-2-phenyl and 2-hydroxy-4-phenylpyrido[1,2-*b*]pyridazinium perchlorates with aqueous KOH afforded **73** and **75** (90JHC1673).



Methylation of the zwitterions **73** and **75** with methyl iodide in boiling acetonitrile or with trimethyloxonium hexafluorophosphate in methylene chloride gave the *O*-methylated products **74** and **76**, respectively (90JHC1673).

Methylation of pyrido[1,2-*b*]cinnolinium-11-olate (**17**,  $R = \text{H}$ ) with the "soft" dimethyl sulfate gave only the *N*-methyl derivative **43** (74JHC125), whereas the "harder" trimethyloxonium tetrafluoroborate yielded the 11-methoxy derivative **77** (92CB929). Methylation of pyrido[2,1-*a*]phthalazinium-7-olate (**20**) with methyl iodide afforded a 1:9 mixture of the

*N*-methyl **78** and 7-methoxy derivatives **79**, whereas dimethyl sulfate and trimethyloxonium tetrafluoroborate gave only the 7-methoxy derivative **79** (92CB929). Although the 11-methoxy derivative **77** could be rearranged to the *N*-methyl derivative **43** by heating in a mixture of toluene and DMF for 17 h in the presence of a small amount of pyrido[1,2-*b*]cinnolinium-11-olate (**17**, R = H), no isomerization to the *N*-methyl derivative **78** occurred when the 7-methoxy compound **79** was heated in the presence of pyrido[2,1-*a*]phthalazinium-7-olate (**20**) (92CB929).

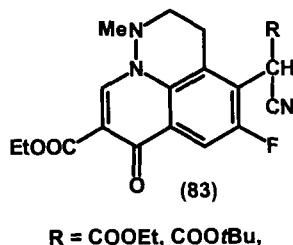
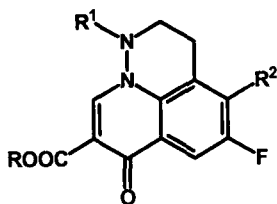
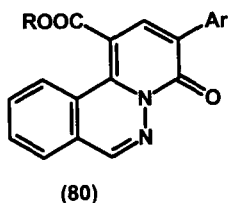


Alkylation of 11-mercaptopyrido[1,2-*b*]cinnolin-6-ium hydroxide inner salts (e.g., **41**) with ethyl bromoacetate gave 11-(ethoxycarbonylmethyl)(thio derivatives **64** (R = H), which could be hydrolyzed to the 11-(carboxymethyl)thio derivative or back to the starting compound **41** (74JHC125). Hydrolysis of the 11-bis(methoxycarbonylmethylene **66** (R = H), and 2-cyano derivatives of **17** (R = H) in boiling HCl afforded 11-methyl and 2-carboxylic acid derivatives, respectively (74JHC125). The 2-nitro derivative of **17** (R = H) was reduced to the 2-amino derivative over Pd/C with NaBH<sub>4</sub> in aqueous methanol, and the 2-amino group was acylated with acetic anhydride at 100°C.

Saponification of alkyl or 3-aryl-4-oxo-4H-pyrido[2,1-*a*]phthalazine-1-carboxylates (**80**, R = alkyl) with methanolic sodium hydroxide gave carboxylic acids [87EUP226196; 88EUP294599; 94H(37)239], which were converted to carbonyl chlorides with thionyl chloride; the carbonyl chlorides were reacted with secondary amines to give carboxamides (87EUP226196; 88EUP294599). The last products also can be prepared from the 1-ester **80** (R = alkyl) (87EUP226196; 88EUP294599).

The 8-ester group of 7-oxopyrido[3,2,1-*ij*]cinnoline-8-carboxylates (**68**, R<sup>3</sup> ≠ H) was hydrolyzed under basic or acidic conditions. The carboxyl group of **68** (R<sup>3</sup> = H) was esterified and the carboxyl group was converted to a boron complex (**70**) by treatment with the boron trifluoride–ether complex (92EUP470578).

The 1-hydroxymethyl group of 1-hydroxymethyl-7-oxo-1*H*,7*H*-pyrido[3,2,1-*ij*]cinnoline-8-carboxylate (**81**) was *O*-alkylated by treatment with diethylaminosulfur trichloride and an alcohol in THF. The 4-hydroxy group of 4-hydroxy-7-oxo-1*H*,7*H*-pyrido[3,2,1-*ij*]cinnoline-8-carboxylate

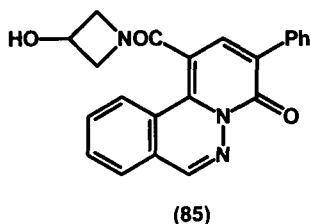
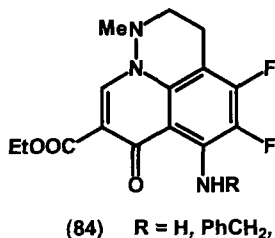


(82) was acylated with methanesulfonyl chloride in pyridine, and the 4-methanesulfonyloxy group was converted to another sulfonyloxy group (92EUP470578).

Heating ethyl 5-fluoro-4-[cyano(ethoxycarbonyl)methyl]-2,3-dihydro-1-methyl-7-oxo-1*H*,7*H*-pyrido[3,2,1-*ij*]cinnoline-8-carboxylate (**83**,  $R = \text{COOEt}$ ) in a mixture of conc. HCl and acetic acid gave the 8-carboxy-4-acetic acid derivative (92EUP470578). The acetic acid group was decarboxylated by heating in boiling ethanol in the presence of  $\text{NEt}_3$  to give the 4-methyl derivative. When the 4-[cyano(*tert*-butoxycarbonyl)methyl]-8-carboxylate **83** ( $R = \text{COOtBu}$ ) was treated with trifluoroacetic acid in methylene chloride at room temperature, the 4-cyanomethyl-8-carboxylate **83** ( $R = \text{H}$ ) was obtained.

Dimethyl dihydrogen 5,6,7,8-tetrahydro-4*aH*-pyrido[1,2-*b*]pyridazine-5,6,7,8-tetracarboxylate was reacted with diazomethane to give the tetraester (63T1237).

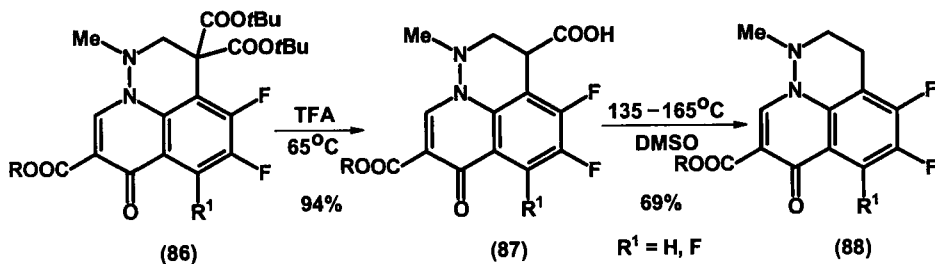
Ethyl 6-amino-4,5-difluoro-1-methyl-7-oxo-1*H*,7*H*-pyrido[3,2,1-*ij*]cinnoline-8-carboxylate (**84**,  $R = \text{H}$ ) was prepared from the 6-benzylamino derivative **84** ( $R = \text{CH}_2\text{Ph}$ ) by catalytic debenzylation over Pd/C in a mixture of ethanol and acetic acid (92EUP470578, 92MIP1).



The hydroxy group of 1-[3-hydroxyazetidin-1-yl]carbonyl]-3-phenyl-4-oxo-4*H*-pyrido[2,1-*a*]phthalazine (**85**) was *O*-methylated with methyl iodide in DMF in the presence of potassium carbonate (87EUP226196).

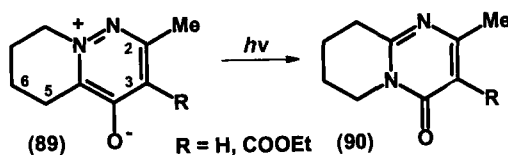
Nonaqueous hydrolysis of pyrido[3,2,1-*ij*]cinnoline-3,3,8-tricarboxylate (**86**) in TFA gave 8-ester-3-carboxylic acid derivative (**87**,  $R = \text{Et}$ )

(92EUP470578, 92MIP1; 95JOC3928). When **87** ( $R = \text{Et}$ ) was heated in acetic acid in the presence of 6 *N* hydrochloric acid to reflux, 3,8-dicarboxylic acid (**87**,  $R = \text{H}$ ) was obtained. The 3-carboxylic group of compound **87** ( $R = \text{H}$ ) was decarboxylated by heating in DMSO to afford **88** ( $R = \text{H}$ ).

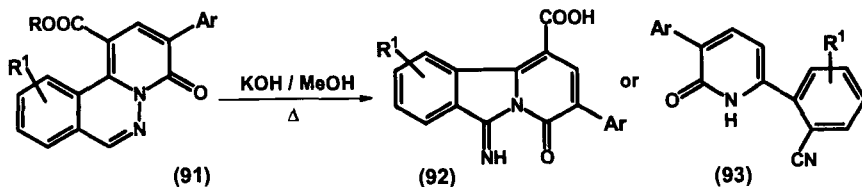


## 6. Ring Transformation

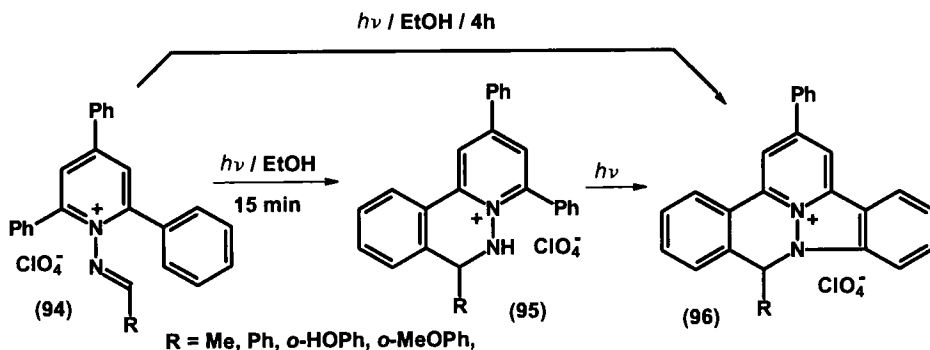
Photolysis of the zwitterionic pyrido[1,2-*b*]pyridazines (**89**) and their 5,6-benzo and 2,3-tetramethylene derivatives afforded 6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (**90**) and their 8,9-benzo [77H(8)377] and 2,3-tetramethylene derivatives (75JOC2201). Photoinduced ring transformation of 2-phenylpyrido[1,2-*b*]pyridazinium-4-olate (**73**) was investigated in methanol (94T4699).



Heating of 4-oxo-4*H*-pyrido[2,1-*a*]phthalazine-1-carboxylic acids or their esters (**91**) in methanolic potassium hydroxide or sodium methoxide yielded either 6-imino-4-oxo-6*H*-pyrido[2,1-*a*]isoindole-1-carboxylic acid (**92**) or ring-opened products (**93**) [92EUP472166; 94H(37)239].



Pentacyclic compounds **96** were obtained by the irradiation of pyrido[2,1-*a*]phthalazine derivatives **95** in ethanol. Compounds **96** were also prepared directly from **94** (90MI1).



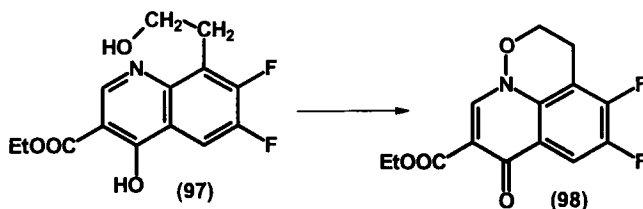
Dimethyl 3-(2-pyridyl)-4-oxo-3,4-dihydroquinoline-2,3-dicarboxylate was obtained from pyrido[1,2-*b*]cinnolin-6-ium hydroxide inner salt **17** (R = H) by reaction with dimethyl acetylenedicarboxylate (75JOC2201).

## IV. Synthesis

### A. PYRIDO[1,2-*b*][1,2]OXAZINES AND THEIR BENZO DERIVATIVES

#### 1. By Formation of One Bond $\alpha$ to the Bridgehead Nitrogen Atom [6 + 0( $\alpha$ )]

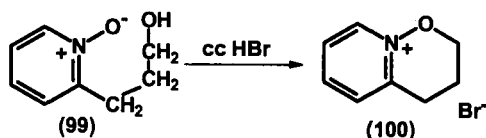
Ethyl 4,5-difluoro-7-oxo-2,3-dihydro-7*H*-pyrido[3,2,1-*ij*][2,1]benzoxazinone-6-carboxylate (**98**) was formed when ethyl 6,7-fluoro-4-hydroxy-8-(2-hydroxyethyl)quinoline-3-carboxylate (**97**) was treated with *m*-chloroperoxybenzoic acid in chloroform [92JAP(K)92/208287, 92JAP(K)92/210656].





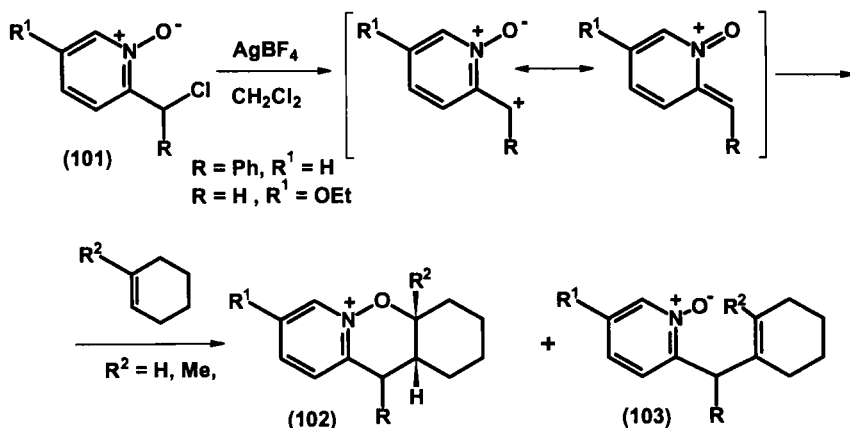
## 2. By Formation of One Bond $\beta$ to the Bridgehead Nitrogen Atom [6 + 0( $\beta$ )]

2,3-Dihydro-4*H*-pyrido[1,2-*b*][1,2]oxazinium bromide (**100**) was obtained when 2-(3-hydroxypropyl)pyridine *N*-oxide (**99**) was heated in 48% aqueous hydrobromic acid under reflux (58JA2217).

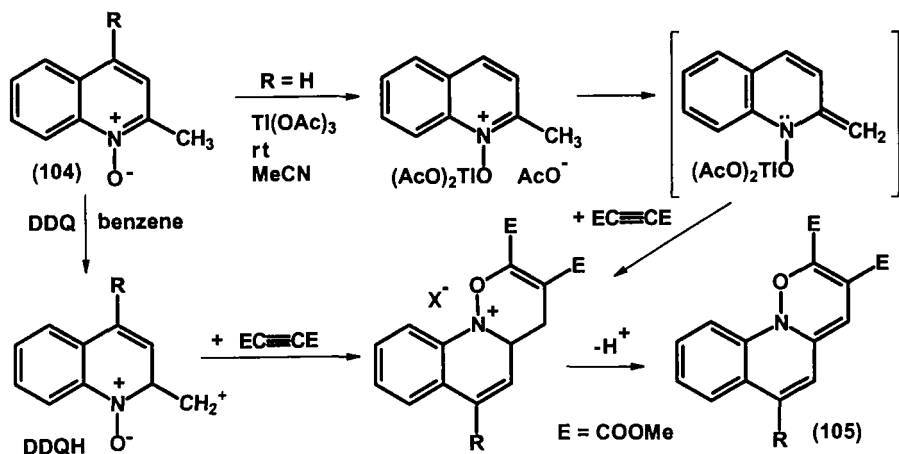


## 3. By Formation of Two Bonds from [4 + 2] Atom Fragments

A  $\text{Ag}^+$ -induced dipolar cycloaddition of 2-chloromethylpyridine *N*-oxides (**101**) with cyclohexenes in the presence of silver tetrafluoroborate afforded a mixture of cycloadducts **102** and substitution products **103** (81AGE481). In some cases, the cycloadduct could be detected only by NMR spectroscopy.

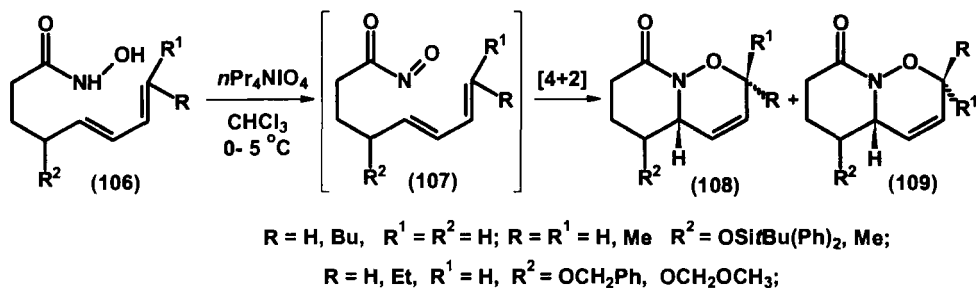


Quinaldine *N*-oxides (**104**) underwent oxidative 1,4-dipolar cycloaddition with dimethyl acetylenedicarboxylate on treatment with  $\text{Ti(III)(OAc)}_3$  or with DDQ to give [1,2]oxazino[2,3-*a*]quinoline-2,3-dicarboxylates (**105**) in low yields [86H(24)1095].



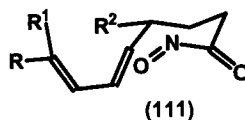
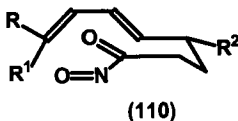
#### 4. Miscellaneous

An intramolecular hetero Diels–Alder reaction of chiral or racemic *N*-acyl nitroso derivatives **107**, prepared from hydroxamic acids **106**, gave a mixture of chiral or racemic pyrido[1,2-*b*][1,2]oxazin-8-ones **108** and **109** in high yields. While  $\omega$ -substituted hydroxamic acid **106** ( $\text{R} = \text{Bu}$ ,  $\text{R}^1 = \text{R}^2 = \text{H}$ ) afforded a single stereoisomer **108** ( $\text{R} = \text{Bu}$ ,  $\text{R}^1 = \text{R}^2 = \text{H}$ ) (85JA5534; 89JOC4088), 4-substituted hydroxamic acids **106** ( $\text{R} = \text{R}^1 = \text{H}$ ,  $\text{Me}$ ,  $\text{R}^2 \neq \text{H}$ ) led to mixtures of epimers **108** ( $\text{R} = \text{R}^1 = \text{H}$ ,  $\text{Me}$ ,  $\text{R}^2 = \text{H}$ ) and **109** ( $\text{R} = \text{R}^1 = \text{H}$ ,  $\text{Me}$ ,  $\text{R}^2 \neq \text{H}$ ), usually with a slight excess of the *trans* compound **108** under nonaqueous conditions [91JCS(CC)1237, 91TL4325; 92JOC2876; 93JOC6083; 94JOC1358, 94TL9213]. The *trans* stereoselectiv-



ity slightly depended on the reaction temperature (93JOC6083), but the low level of *trans* stereoselectivity was improved when reactions were carried out in water under heterogeneous conditions [94JOC1358, 94TL595;

96JCS(P1)1113]. The formation of the *trans* adduct involves a boatlike endo transition state (**110** versus **111**), which is enhanced in aqueous solution by some extra charge separation resulting from both secondary orbital interaction and by a hydrophobic packing effect of the substrate (94JOC1358, 94TL595).



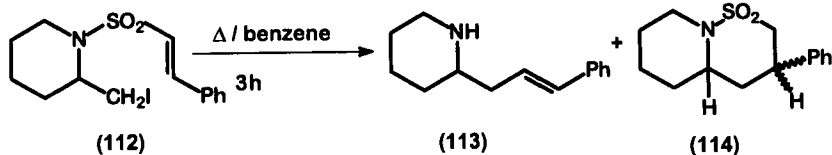
### B. PYRIDO[1,2-*b*][1,2]THIAZINES

#### 1. By Formation of One Bond $\alpha$ to the Bridgehead Nitrogen Atom [ $6 + 0(\alpha)$ ]

Perhydropyrido[1,2-*b*][1,2]thiazine-1,1-dioxide was prepared in 70% yield by the cyclization of 2-(3-chlorosulfonylpropyl)piperidine hydrochloride, obtained from *S*-[3-(2-piperidyl)propyl]isothiourea dihydrochlorides with chlorine gas, on heating in toluene (62AP615).

#### 2. By Formation of One Bond $\gamma$ to the Bridgehead Nitrogen Atom [ $6 + 0(\gamma)$ ]

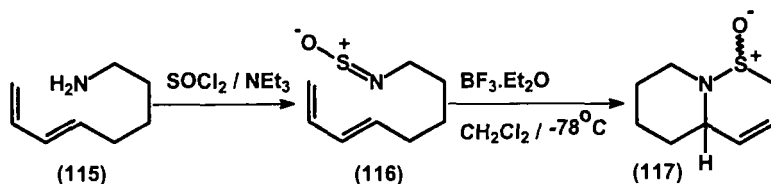
In a radical reaction of 2-iodomethylpiperidine (**112**) with tributyltin hydride, 2-(3-phenyl-2-propenyl)piperidine (**113**) and a 1 : 1 mixture of epimers of perhydropyrido[1,2-*b*][1,2]thiazine-1,1-dioxide (**114**) were obtained in 18 and 47% yield, respectively (77TL635). An identical mixture of **113** and the two epimers of **114** was also obtained from a 7 : 4 mixture of the *Z* and *E* isomers of **112**, indicating that the starting C=C geometry is not maintained in the product **114**.



#### 3. Miscellaneous

An intermolecular Diels-Alder reaction of the *N*-sulfinyl diene **116**, prepared from amino diene **115**, gave a 1 : 2 mixture of epimers of 1-

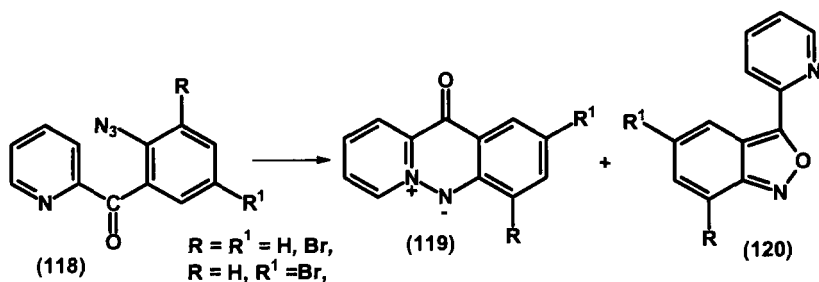
oxypyrido[1,2-*b*][1,2]thiazine (**117**) in 40% yield (88TL4233). No [4 + 2] cycloaddition occurred under thermal conditions, but at 12 kbar the same mixture of **117** was produced in a higher yield (82%).



### C. PYRIDO[1,2-*b*]PYRIDAZINES AND THEIR BENZO DERIVATIVES

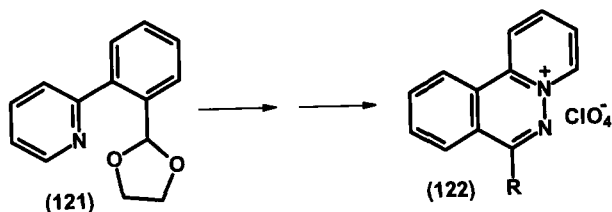
#### 1. By Formation of One Bond $\alpha$ to the Bridgehead Nitrogen Atom [ $6 + 0(\alpha)$ ]

The pyrolysis of 2-(2-azido-3,5-dibromobenzoyl)pyridine (**118**,  $R = R^1 = \text{Br}$ ) in 1,2,4-trichlorobenzene for 24 h yielded 2,4-dibromo-11-oxypyrido[1,2-*b*]cinnolin-6-ium hydroxide inner salt (**119**,  $R = R^1 = \text{Br}$ ) in 85% yield (74JHC125). The pyrolysis in boiling toluene gave a ca. 1:1 mixture of 5,7-dibromo-3-(2-pyridyl)-2,1-benzisoxazole (**120**,  $R = R^1 = \text{Br}$ ) and the foregoing tricyclic derivative.

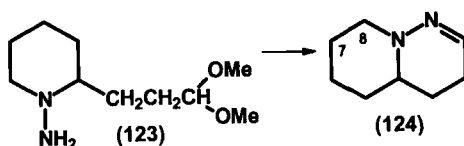


#### 2. By Formation of One Bond $\beta$ to the Bridgehead Nitrogen Atom [ $6 + 0(\beta)$ ]

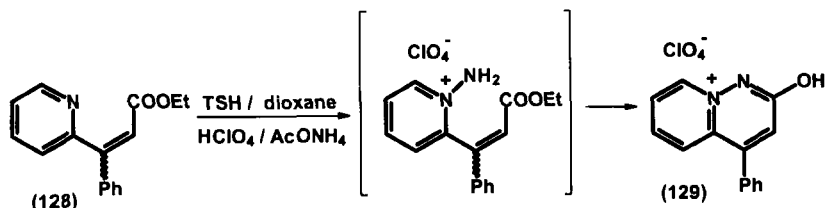
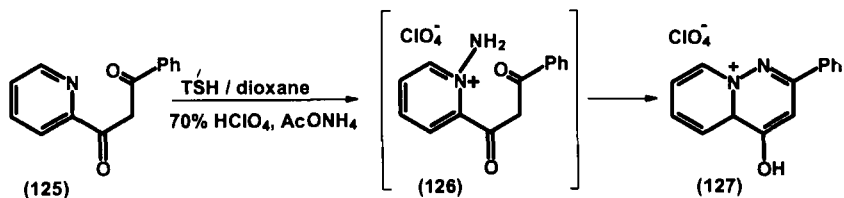
*N*-Amination of 2-[*o*-(1,3-dioxolan-1-yl)phenyl]pyridine (**121**) with *O*-tosylhydroxylamine gave an *N*-amino derivative, which underwent ring closure on the action of 70% perchloric acid to yield a pyrido[2,1-*a*]phthalazinium salt (**122**,  $R = \text{H}$ ) (92JHC1049). The 7-hydroxy derivative of a pyrido[2,1-*a*]phthalalzinium salt (**122**,  $R = \text{OH}$ ) was prepared similarly by cyclization of 1-amino-2-(*o*-methoxycarbonylphenyl)pyridinium salt, ob-



tained from 2-(*o*-methoxycarbonylphenyl)pyridine by reaction with *O*-tosylhydroxylamine (92CB929), 3-(1-Amino-2-piperidyl)propionaldehyde dimethyl acetal (**123**) was cyclized to 4,4a,5,6,7,8-hexahydro-3*H*-pyrido [1,2-*b*]pyridazine (**124**) in boiling ethanol in the presence of oxalic acid (68YZ216). 3,4,5,6-Tetrahydro-4*aH*-pyridazino[1,6-*a*]quinoline (7,8-benzolog of **124**) was prepared similarly (66YZ608). Reduction of 3-(*N*-nitroso-2-piperidyl)propionic acid with Zn dust in 85% acetic acid (65MI1, 65URP170506; 66KGS91), or of its ethyl ester (78JA4012) in water over Pd on calcium carbonate with hydrogen, in the presence of  $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$  afforded 3-(*N*-amino-2-piperidyl)propionic acid and its ethyl ester, respectively, which underwent spontaneous cyclization to give perhydropyr-ido[1,2-*b*]pyridazin-2-one.

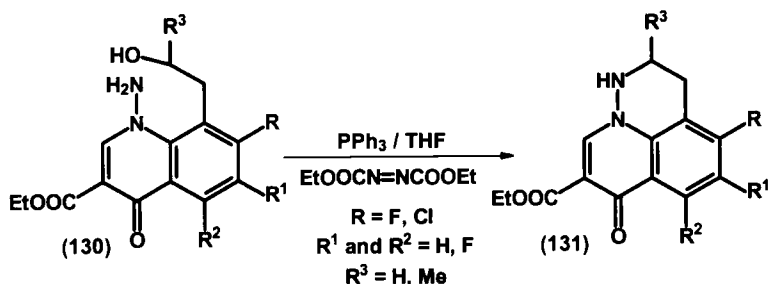


2-Acylpyridine (**125**) was *N*-aminated with *O*-tosylhydroxylamine (TSH), and the *N*-amine formed (**126**) was cyclized on the action of 70% perchloric

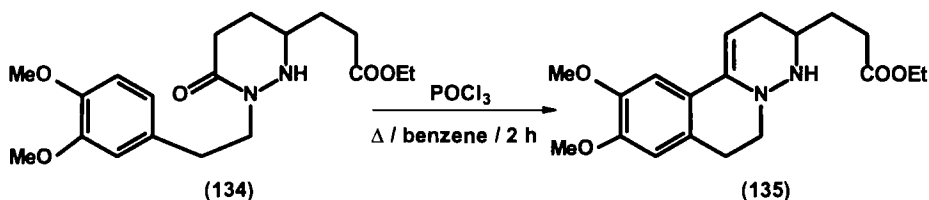
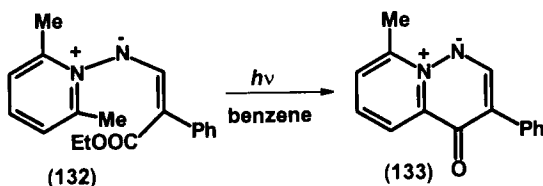


acid to yield a 4-hydroxypyrido[1,2-*b*]pyridazinium salt (**127**), from which zwitterion **73** was obtained by treatment with 11% aqueous potassium hydroxide in ethanol (90JHC1673). Isomeric pyrido[1,2-*b*]pyridazinium-2-olate (**75**) was prepared similarly, starting from a 1:1 mixture of the *E* and *Z* isomers of **128**, via **129**.

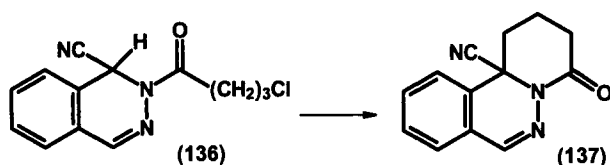
Cyclization of 1-amino-8-(2-hydroxyalkyl)-4-oxoquinoline-3-carboxylates (**130**) on the action of diethyl azodicarboxylate in the presence of triphenylphosphine afforded 7-oxopyrido[3,2,1-*ij*]cinnoline-8-carboxylates (**131**) (92EUP470578).



Photolysis of *N*-ylide **132** gave a complex reaction mixture, from which pyrido[1,2-*b*]pyridazin-4-one **133** could be isolated in 15% yield (76JOC1570).

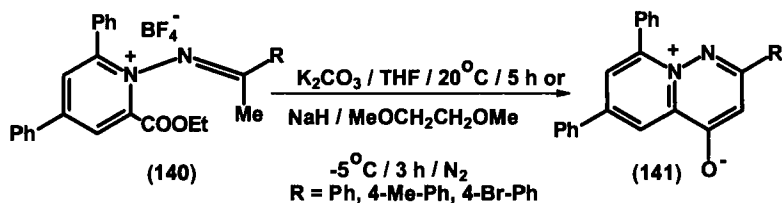
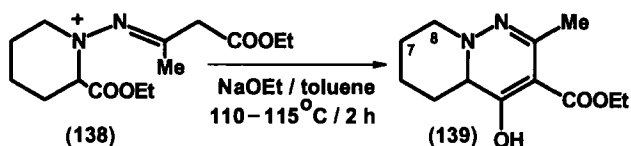


Bischler-Napieralski cyclization of pyridazin-6-one **134** with  $\text{POCl}_3$ , and subsequent hydrogenation of the cyclized product **135** over  $\text{PtO}_2$ , gave rise to 2,3,4,6,7,11*b*-hexahydro-1*H*-pyridazino[6,1-*a*]isoquinoline (**51**) (75CPB3056). Treatment of Reissert compound **136** with  $\text{NaH}$  gave 11*b*-cyano-1,2,3,11*b*-tetrahydro-4*H*-pyrido[2,1-*a*]phthalazin-4-one (**137**) (80JHC433).



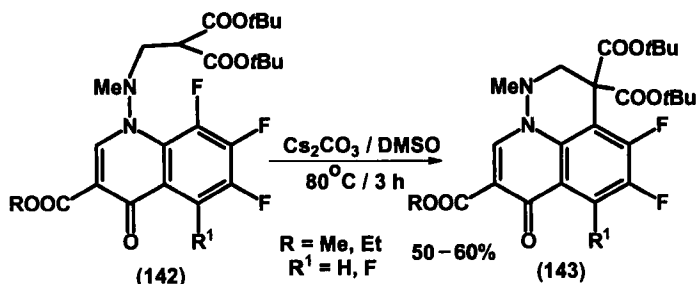
3. *By Formation of One Bond  $\gamma$  to the Bridgehead Nitrogen Atom [6 + 0( $\gamma$ )]*

Dieckmann condensation of piperidine-2-carboxylate **138** in toluene in the presence of NaOEt furnished pyrido[1,2-*b*]pyridazine-3-carboxylate (**139**) (71CPB159). Ethyl 2-methyl-4-hydroxy-5,6-dihydro-4*aH*-pyridazino[1,6-*a*]quinoline-3-carboxylate (7,8-benzolog of **139**) was prepared similarly (66YZ613).



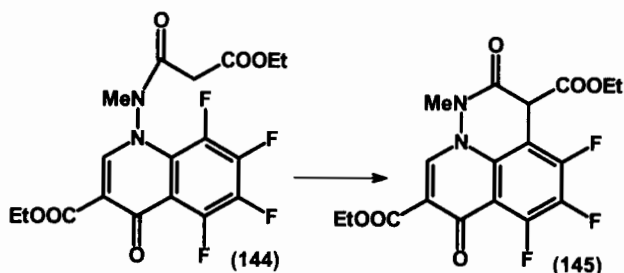
Treatment of pyridinium salts **140** either with  $\text{K}_2\text{CO}_3$  or with NaH afforded 4-oxidopyrido[1,2-*b*]pyridazinium zwitterions **141** [81JCS(P1) 1495].

Brief photocyclization of pyridinium derivative **94** afforded 2,4-diphenyl-7-substituted 5,6-dihydropyrido[2,1-*a*]phthalazinium salts (**95**) (95IZV296).



Cyclization of 1-[*N*{2,2-bis(*tert*)-butyloxycarbonyl}ethyl]-*N*-methyl-amino]-5,6,7,8-tetrafluoro-4-oxoquinoline-3-carboxylates (**142**,  $R^1 = F$ ) in the presence of  $Cs_2CO_3$  gave 7-oxopyrido[3,2,1-*ij*]cinnoline-3,3,8-tricarboxylates (**143**) (92EUP470578, 92MIP1; 95JOC3928; 96JCS(CC)61). The cyclization was accompanied by some N—N bond cleavage (5–20%).

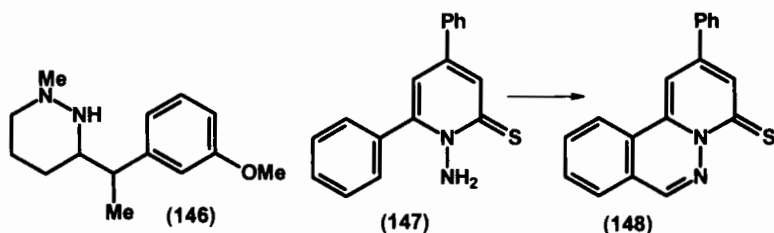
2,7-Dioxopyrido[3,2,1-*ij*]cinnoline-3,8-dicarboxylate (**145**) was obtained by the cyclization of quinoline-3-carboxylate (**144**) (92MIP1).



#### 4. By Formation of Two Bonds from [5 + 1] Atom Fragments

Cyclization of the hydrochloride of 1-methyl-3-[1-(*m*-methoxyphenyl)ethyl]perhydropyridazine (**146**) with formaldehyde and hydrochloric acid gave 1,5-dimethyl-7-methoxy-1,2,3,4,5,10-hexahydro-4*aH*-pyridazino[1,6-*b*]isoquinoline (**22**) (73JHC999).

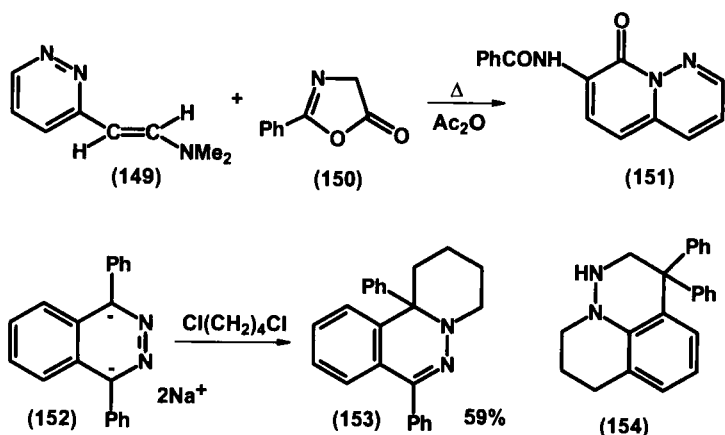
The reaction of 1-amino-4,6-diphenylpyridine-2(1*H*)-thione (**147**) with dimethylformamide dimethyl acetal or triethyl orthoformate afforded 2-phenyl-4*H*-pyrido[2,1-*a*]phthalazine-4-thione (**148**) [81AQ(C)248].



#### 5. By Formation of Two Bonds from [4 + 2] Atom Fragments

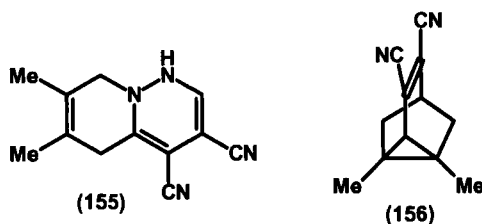
The reaction of 2-phenyl-5(4*H*)-oxazolone (**150**) and 3-[(*E*)-2-*N,N*-dimethylaminoethenyl]pyridazine (**149**) in boiling acetic acid afforded 7-benzamido-8*H*-pyrido[1,2-*b*]pyridazin-8-one (**151**) (91BSB533). Treatment of dianion **152** with 1,4-dichlorobutane at  $-78^\circ C$  gave 7,11*b*-diphenyl-2,3,4,11*b*-tetrahydro-1*H*-pyrido[2,1-*a*]phthalazine (**153**) (86JHC13).





The reaction between 1,1-diphenylethene and 1-imino-1,2,3,4-tetrahydroquinolinium ion, obtained by electrochemical oxidation of 1-amino-1,2,3,4-tetrahydroquinoline, furnished 3,3-diphenyl-1,2,3,7,8,9-hexahydro-pyrido[3,2,1-*ij*]cinnoline (66TL2583).

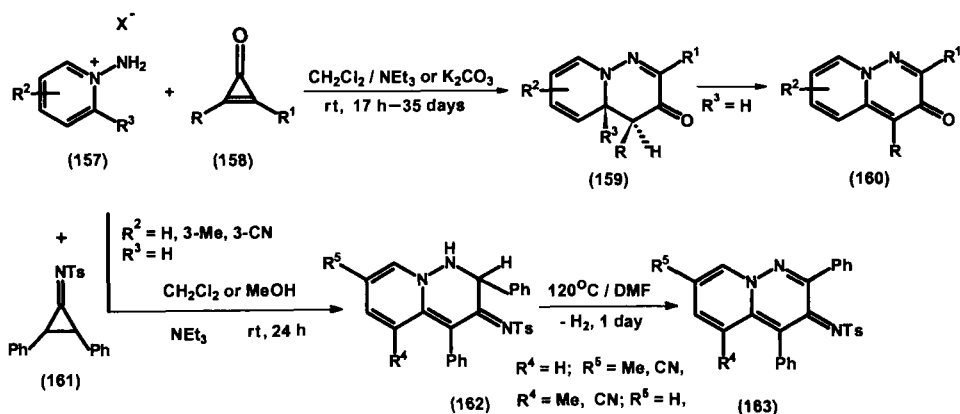
The reaction of 4,5-dicyanopyridazine with 2,3-dimethylbuta-1,3-diene in chloroform in a sealed tube at  $110^\circ\text{C}$  gave a mixture of nitrogen bridge-head compounds **26** (8%) and **155** (11%), and a tricyclo[3.2.10<sup>2,7</sup>]oct-3-ene (**156**) (64%) in [2 + 4] and [4 + 2] cycloaddition processes, respectively (94T9189).



## 6. By Formation of Two Bonds from [3 + 3] Atom Fragments

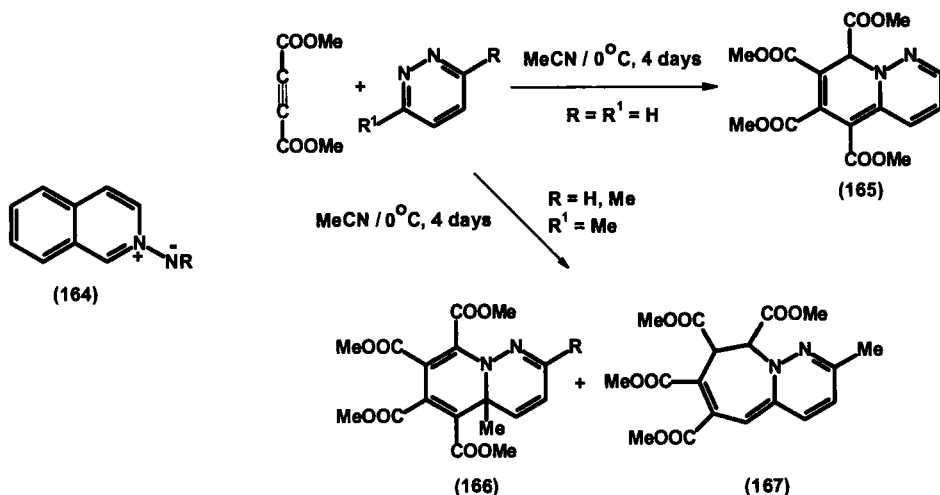
When pyridinium *N*-imine salts **157** were reacted with methylphenylcyclopropenone (**158**,  $\text{R} = \text{Ph}$ ,  $\text{R}^1 = \text{Me}$ ) in the presence of a base, dihydropyrido[1,2-*b*]pyridazin-3-ones (**159**) were formed, which subsequently underwent oxidation to produce 3*H*-pyrido[1,2-*b*]pyridazin-3-ones (**160**) under the reaction conditions [76JCS(CC)275; 78JOC2892]. In some cases the dihydro intermediates (**159**) could be isolated. 3-Substituted derivatives (**157**,  $\text{R}^2 = 3\text{-Me}$ ,  $3\text{-CN}$ ;  $\text{R}^3 = \text{H}$ ) gave mixtures of isomers of **160** ( $\text{R}^2 = 5\text{-}$

and 7-Me and CN). When the reaction was carried out in methanol, the resulting pyrido[1,2-*b*]pyridazin-3-one (**160**,  $R = \text{Ph}$ ,  $R^1 = \text{Me}$ ,  $R^2 = \text{H}$ ) was accompanied by methyl  $\alpha$ -methyl- $\beta$ -amino-*trans*-cinnamate as by-product in 31% yield. Di-*n*-propylcyclopropenone (**158**,  $R = R^1 = n\text{Pr}$ ) did not react with pyridinium *N*-imine salts (**157**,  $R^3 = \text{H}$ ) in methanol in the presence of an excess of  $\text{NEt}_3$  at room temperature, but reaction did occur under reflux for 2–12 days to give pyrido[1,2-*b*]pyridazin-3-ones (**160**,  $R = R^1 = n\text{Pr}$ ) (78JOC2892). Pyridinium *N*-imine salt **157** ( $R^2 = R^3 = \text{H}$ ) reacted



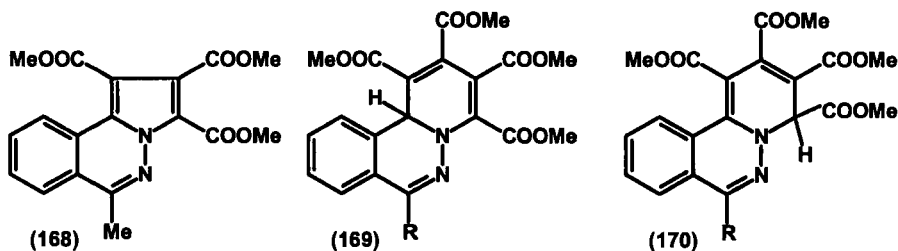
with diphenylcyclopropenone (**158**,  $R = R^1 = \text{Ph}$ ) as a nucleophilic reagent, but not as a 1,3-dipolar one, to yield only  $\alpha$ -phenyl- $\beta$ -amino-*trans*-cinnamate (75JOC2985). However, when pyridinium *N*-imine salts **157** were reacted with *N*-(*p*-toluenesulfonyl)diphenylcyclopropenimine (**161**), 3-iminopyrido[1,2-*b*]pyridazines (**163**) were obtained. In the case of 3-methylpyridinium *N*-amino iodide (**157**,  $R^2 = 3\text{-Me}$ ,  $R^3 = \text{H}$ ,  $\text{X} = \text{I}$ ), the 1,2-dihydro derivative (**162**,  $R^4 = \text{Me}$ ,  $R^5 = \text{H}$ ) could also be isolated, which was dehydrogenated to **163** ( $R^4 = \text{Me}$ ,  $R^5 = \text{H}$ ) by heating in DMF [84H(22)1709].

From reaction mixtures of isoquinolinium ylides (**164**,  $R = \text{H}$ ,  $\text{COOEt}$ ,  $\text{COPh}$ ), and diphenylcyclopropenone in benzene, the pyridazino[6,1-*a*]isoquinolines **49**, **50**, **55**, and **63** were isolated in 10–33% yields, including 1,3-oxazine-6-ones (83JOC1084). Pyridazino[6,1-*a*]isoquinolin-2-one (**63**) was isomerized into the 2-hydroxy derivative **56**. The reactions of isoquinolinium ylides (**164**,  $R = \text{COOEt}$ ,  $\text{COPh}$ ) with *N*-tosyldiphenylcyclopropenimine led to 4*H*-pyridazino[6,1-*a*]isoquinolines **42** and **54**.



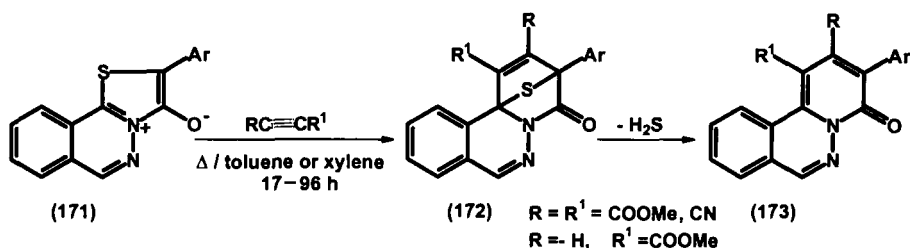
### 7. By Formation of Three Bonds from [2 + 2 + 2] Atom Fragments

The reactions of pyridazines with 2 mol dimethyl acetylenedicarboxylate at 0°C gave tetracarboxylates **165** and **166** [66JCS(C)2218]. At higher temperature (100°C) no reaction occurred, and in methanol the product was a pyrrolo[1,2-*b*]pyridazine derivative (65JCS3200). In the case of 3,6-dimethylpyridazine, the main product was azepino[1,2-*b*]pyridazine (**167**). 1-Methylphthalazine reacted with dimethyl acetylene dicarboxylate in boiling acetonitrile to give a mixture of pyrrolo[2,1-*a*]phthalazine (**168**) and 11*bH*-pyrido[2,1-*a*]phthalazine (**169**, R = Me), with an excess of the latter. Compound **169** (R = Me) was isomerized to **170** (R = Me) under acidic conditions [66JCS(C)2218]. No reaction occurred in the case of 1-methoxyphthalazine. A mixture of 11*bH*- and 1*H*-pyrido[2,1-*a*]phthalazines (**169**, R = H) and (**170**, R = H) was obtained in the reaction of phthalazine and dimethyl acetylenedicarboxylate [68RRC513; 79JCR(S)394].

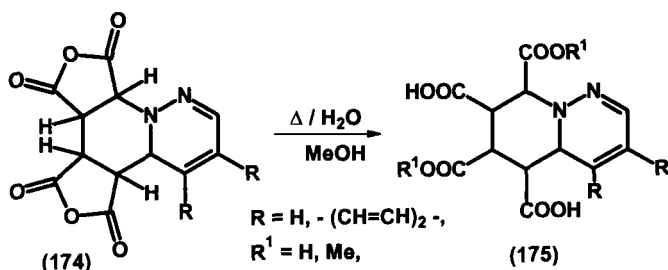


## 8. Ring Transformation

The reactions of *anhydro* 2-aryl-3-hydroxythiazolo[2,3-*a*]phthalizinium hydroxides (**171**) with methyl propiolate (87EUP226196; 88EUP294599), dimethyl acetylenedicarboxylate (85JOC1677), or fumaronitrile (85JOC1677) gave 4*H*-pyrido[2,1-*a*]phthalazin-4-ones (**173**) via cycloadducts **171**. When methyl vinyl ketone was reacted with **171** ( $R = H$ ), in addition to 9% of 4*H*-pyrido[2,1-*a*]phthalazin-4-one (**173**,  $R = H$ ,  $R^1 = \text{COMe}$ ), a cycloadduct was also isolated (85JOC1677).

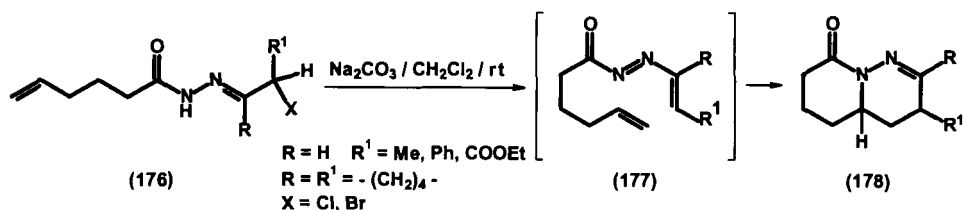


Pyrolysis of 3-(2-pyridyl)-2,1-benzisoxazoles (**120**,  $R = H$ ,  $R^1 = H$ , Br) afforded 11-oxopyrido[1,2-*b*]cinnolin-6-ium hydroxyde inner salts (**119**,  $R = H$ ,  $R^1 = H$ , Br) (74JHC125).



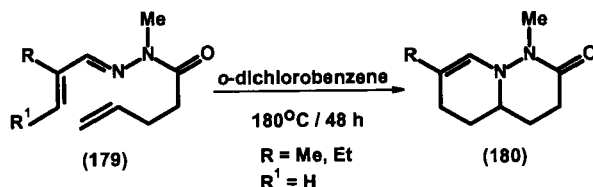
## 9. Miscellaneous

When cycloadducts **174**, obtained in the reaction of pyridazine and phthalazine with maleic anhydride, were subjected to solvolysis with hot

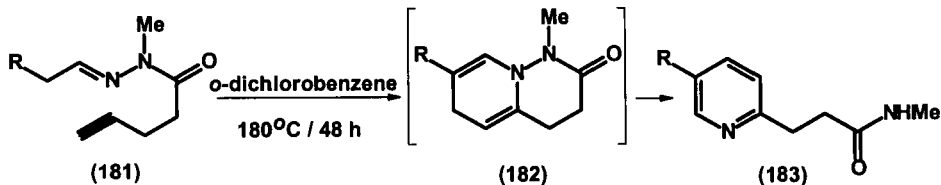


water and methanol, the products were tetracarboxylic acid derivatives **175** (63T1237; 67RRC109).

Hexahydropyrido[1,2-*b*]pyridazin-8-ones **178** and a 2,3-tetramethylene derivative were formed on the intramolecular cycloaddition of **177**, formed *in situ* by dehalogenation of hydrazones of the hex-5-enoic acid derivatives **176** [87JCS(P1)2511]. Intramolecular cycloaddition of hydrazones **179** in



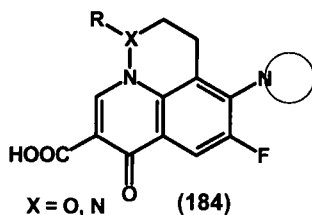
*o*-dichlorobenzene afforded cycloadducts **180** (91T10053, 91TL125). The R = R' = H and R = H, R' = Me derivatives decomposed under the reaction conditions, and the *N*-desmethyl derivative of **179** (R = Me) did not give bicyclic product (91TL125). When the acetylene derivatives (**181**) were the starting materials, the initially formed pyrido[1,2-*b*]pyridazin-2-ones (**182**) were transformed to 3-(2-pyridyl)propionamides (**183**) under the reaction conditions (91T10053, 91TL125).



## V. Applications and Important Compounds

Various perhydropyrido[1,2-*b*][1,2]oxazines were applied as key intermediates in a stereospecific total syntheses of (±)-indolizidine 223AB (85JA5534; 89JOC4088), (–)-indolizidines 205A, 207A, 209B, and 235B [91JCS(CC)1237; 92JOC2876], (±)-dihydropinidine (89JOC4088), (±)-monomorine I and epimonomorine I (86TL5513; 89JOC4088), (–)-nupharamine and (+)-3-epinupharamine (91TL4325), (–)-swainsonine (94JOC1358) and its 8- and 8*a*-epimers (93JOC6083), and (–)-pumiliotoxin C [94TL9213; 96JCS(P1)1113] and its 5-epimer [96JCS(P1)1113] alkaloids.

2,3-Dihydro-4*H*-pyrido[1,2-*b*][1,2]oxazine is claimed to have been used as an organic oxyradical in the photocleavage of DNA and similar oligomers having a sugar–phosphate backbone (93MIP1).



4-(Substituted amino)-5-fluoro-7-oxo-3,7-dihydro-2*H*-pyrido[3,2,1-*ij*][2,1]benzoxazine-8-carboxylic acids (**184**, X = O) [92JAP(K)92/208287, 92JAP(K)92/208288, 92JAP(K)92/210656] and 4-(substituted amino)-5-fluoro-7-oxo-1,2,3,7-tetrahydropyrido-[3,2,1-*ij*]cinnoline-8-carboxylic acids (**184**, X = N) are patented as effective antimicrobial agents against gram-positive and gram-negative bacterial infections [92EUP470578, 92MIP1; 93JAP(K)93/213951].

## Appendix

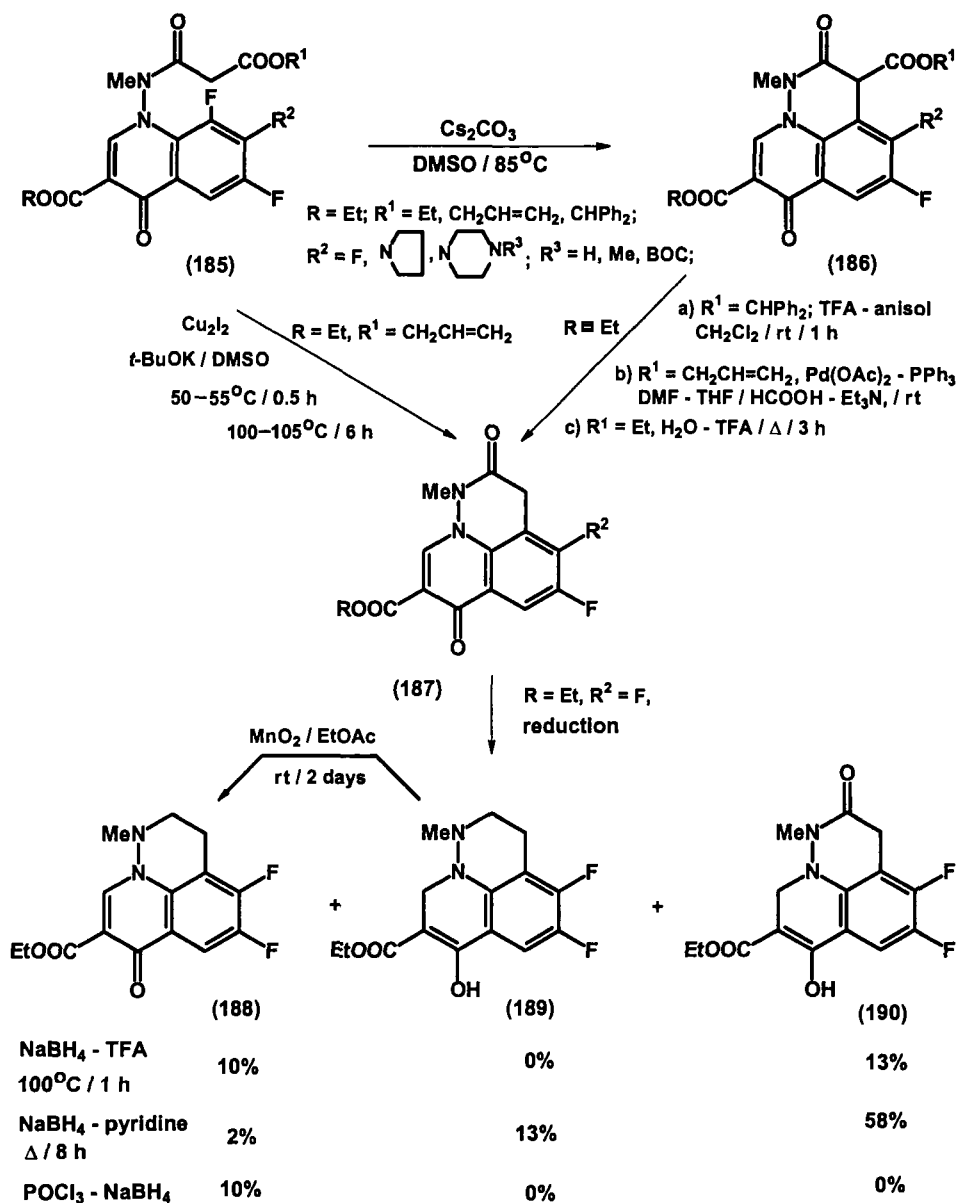
The crystal structure of ethyl 4-(4-*tert*-butoxycarbonyl-1-piperazinyl)-5-fluoro-2,3-dihydro-1-methyl-2,7-dioxo-1*H*,7*H*-pyrido[3,2,1-*ij*]cinnoline-8-carboxylate (**186**, R = Et, R<sup>1</sup> = *tert*-Bu, R<sup>2</sup> = 4-*tert*-butoxycarbonyl-1-piperazinyl) was determined by means of X-ray diffraction investigation [95T11125].

Reduction of **187** (R = Et, R<sup>2</sup> = F) with NaBH<sub>4</sub> under various circumstances afforded mixtures of **188** (2–10%), **189** (0–13%), and **190** (0–58%) (see Scheme 4). Oxidation of **189** with activated MnO<sub>2</sub> in ethyl acetate for 2 days at ambient temperature gave **188** in 56% yield [95T11125].

The substitution of a 4-fluoro atom in **187** (R = Et, R<sup>2</sup> = F) with cyclic amines was unsuccessful at 80–120°C, probably because of the presence of an acidic CH<sub>2</sub> group at position 3 [95T11125].

The N(4) atom of the side-chain piperazino group of **187** (R = Et, R<sup>2</sup> = piperazino) was acylated with di-*tert*-butyl oxalate. 3-Decarboxylated products (**187**) were prepared from **186** under different reaction conditions in 44–81% yield (see Scheme 4) [95T11125]. The ester group of **187**(R = Et) was hydrolyzed in boiling acetic acid in the presence of concentrated hydrochloric acid to give 3-carboxylic acids (**187**, R = H).

Cyclization of quinoline derivatives **185** in DMSO on the action of cesium carboxate at 85°C afforded diesters **186** [95T11125]. No cyclization product could be obtained when a piperazono group was present in **185** (R<sup>2</sup> = piperazino). Cyclization in the presence of sodium hydride gave lower yield. When the potassium salt of **185** was applied in the presence of 20 mol%



SCHEME 4

of cuprous iodide, the conversion was almost quantitative, but the removal of the trace of copper was difficult. When allyl ester (**185**, R = Et, R<sup>1</sup> = allyl, R<sup>2</sup> = 4-*tert*-butoxycarbonyl-1-piperidinyl) was cyclized in DMSO in the

presence of cuprous iodide and potassium *tert*-butoxide at 50–55°C for 0.5 h, then 100–105°C for 6 h, the 3-ester (**187**, R = Et, R<sup>2</sup> 4-*tert*-butoxycarbonyl-1-piperidiny) was obtained in 32% yield.

### ACKNOWLEDGMENTS

The author thanks Professors Alan R. Katritzky and Gurnos Jones for their encouragement and helpful comments, and Dr. David Durham for linguistic improvements. The invaluable assistance of Mrs. K. Juhász-Kupás and Mrs. J. Baráth-Csutorás throughout the preparation of this manuscript is gratefully acknowledged.

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62AP615  
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65URP170506  
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66KGS91  
66TL2583  
66YZ608  
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## Acyclonucleosides: Part 3. *tri*-, *tetra*-, and *pentaseco*-Nucleosides\*

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This chapter is the third of a sequence of three chapters that appears in successive volumes of this series dealing with the chemistry of acyclonucleosides; the first and second parts appeared in the previous two volumes [96AHC(67)391, 97AHC(68)1] and dealt with *seco*-nucleosides (one bond disconnection) and *diseco*-nucleosides (two bond disconnections), respec-

\* Part 1 can be found in Volume 67; Part 2 appears in Volume 68.

tively. The present chapter deals with *tri*-, *tetra*-, and *penta-seco*-nucleosides and includes an appendix compiling the recent literature that appeared after the three chapters were prepared.

#### IV. *triseco*-Nucleosides from Three Bond Disconnections

##### A. 1',2',-2',3' AND 3',4'-TRISECO-NUCLEOSIDES (TYPE 3.1)

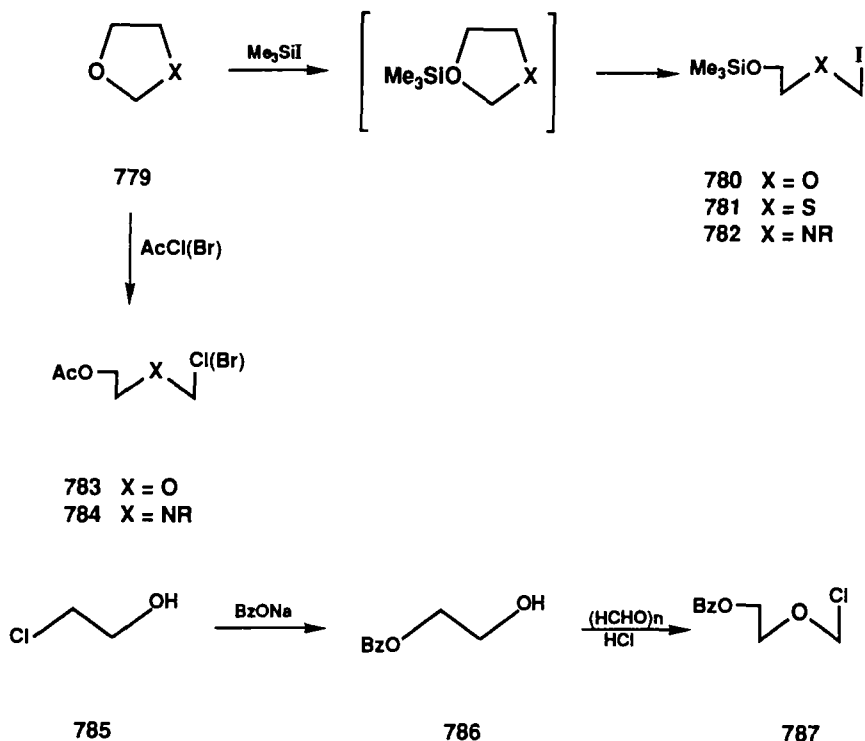
This type of nucleoside represents the first lead for acyclonucleosides. Acyclovir [9-[(2-hydroxyethoxy)methyl]guanine, Zovirax, ACV] was the first member reported to be a potent antiherpetic drug (78NAT583; 83MI2; 85MI1). It inhibited the *in vitro* transformation of NIH 3T3 cells by Abelson murine leukemia virus and the proliferation of abl and bcr-abl-transformed hemopoietic murine cell lines (92JBC22178). It is an active inhibitor of uridine phosphorylase (85MI5; 87MI2). The crystal structure of acyclovir has been determined (84CJC2646). These aspects of biological activity led to a great number of modifications of the structure of ACV.

##### 1. General Methods for Construction

1,3-Dioxolane, 1,3-oxathiolane, or oxazolidine **779** react with trimethylsilyl iodide to afford iodomethyltrimethylsilyloxyethyl ether **780**, thioether **781**, or amine **782**, respectively (79TL3263; 80JMC572; 83AP146). Treatment of **779** with acetyl chloride in the presence of sulfuric acid gave (2-acetoxyethoxy)methyl chloride **783** contaminated with a tenacious by-product. But, treatment of **779** with neat acetyl bromide gave pure (2-acetoxyethoxy)methyl bromide **783** as a readily distilled colorless oil (82CJC547). **784** was similarly prepared. The benzoyloxy derivative **787** was prepared by the reaction of sodium benzoate with chloroethanol **785** to give **786**, whose chloromethylation gave **787** (81JHC947).

Although **787** was originally used for the alkylation of 6-chloropurine, 6-methylthiopurine, and 4-methylthio-2-pyrimidinone (79TL3263), it was not used in later work (82CJC547). However, when bromomethoxy derivative **783** was coupled *in situ* with silylated uracils, it gave after deprotection the corresponding acyclonucleosides **788**. However, the adenine analog was prepared via its anion by coupling with **780** [93JCS(P1)1109].

2,6-Dichloro-9-[2-benzoyloxyethoxymethyl]purine was prepared as a key intermediate, which upon selective substitution of the 6-chloro group by ammonia followed by deamination and then displacement of the 2-chloro group gave 9-(2-hydroxyethoxymethyl)guanine. The use of the same synthetic procedure led to a variety of analogs. Of these ACV was found to



SCHEME 152

have marked antiviral activity in animal models of herpes virus infections associated with very low toxicity [78NAT583; 84JMC1486; 85KFZ1371; 86IJC(B)823, 86MI3; 88MI1, 88MI4, 88MI5; 90EUP3939201; 90MI6, 90MIP1; 91MI5; 94JPR129; 94MI7].

The alkylation of a purine analogs may afford the 7-isomer in addition to the 9-isomer (83AP146; 89MI5). The addition of mercuric cyanide resulted in N-9 coupling. The phase transfer catalyst 18-crown-6 or tetraglyme was used for the alkylation of allopurinol analogs (87MI4). The addition of potassium iodide to the alkylation mixture allows mild condensation conditions (89MI12).

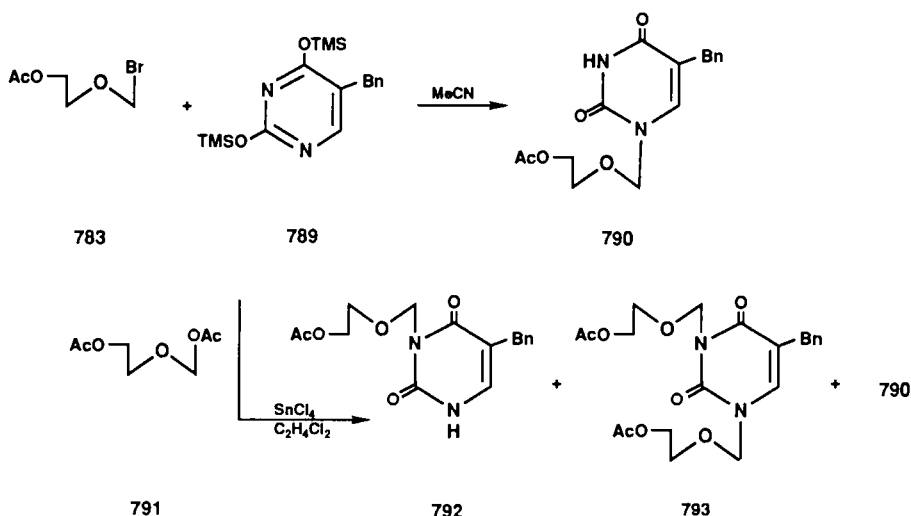
Variation of the ring portion of acyclovir has been achieved. Compounds include monocyclic (isocytosine, triazole, imidazole), bicyclic (adenine, 8-azapurine, pyrrolo[2,3-*d*]-pyrimidine, pyrazolo[3,4-*d*]pyrimidine, indole, benzotriazole) and tricyclic (linear benzoguanine) congeners (86JHC289;



substituted analogs were prepared. Displacement of the 4-ethoxy group by amines gave cytosine analogs (81JMC753). Bromination or iodination of uracil analogs gave the 5-halogeno derivatives. These derivatives exhibit little or no activity against herpes simplex virus type 1 or against a range of other DNA and RNA viruses. Various derivatives of uracil and pyrimidine acyclic nucleosides were prepared (84JMC1486; 85MI2; 86CS179; 88CL1045, 88H71; 89MIP1; 91MI1). The pyrimidine acyclonucleosides are reported to be competitive inhibitors of uridine phosphorylase but have no effect on thymidine phosphorylase, uridine kinase, or thymidine kinase (81MI1). The tritium-labeled *N*-[2-(hydroxyethoxy)methyl]-5-[<sup>3</sup>H]methyluracil was prepared for evaluation as a tumor diagnostic agent (85MI3).

Coupling of persilylated 6-azauracils (as-triazine) derivatives with **783** gave the respective nucleosides (85MI4; 89MI7; 91MI14; 93MI15). The triazine oxide and its benzo derivative were also used in the coupling (82JHC497; 86JHC1613). The acyclonucleoside analog of pentostatin was also prepared (83JMC1478).

Reaction of the silyl derivative of quinoline with 2-acetoxyethyl acetoxy-methyl ether in dichloroethane with stannic chloride gave a cyclonucleoside. Removal of both the acetyl and ethyl ester groups in NaOH afforded the fully deprotected nucleoside **788**. Acylation of **788** could be carried out with different esters in the presence of amino Ps lipase [91SC1477; 92JCR(S)216]. The 4-quinolones showed no significant antiviral activity (91SC1477).



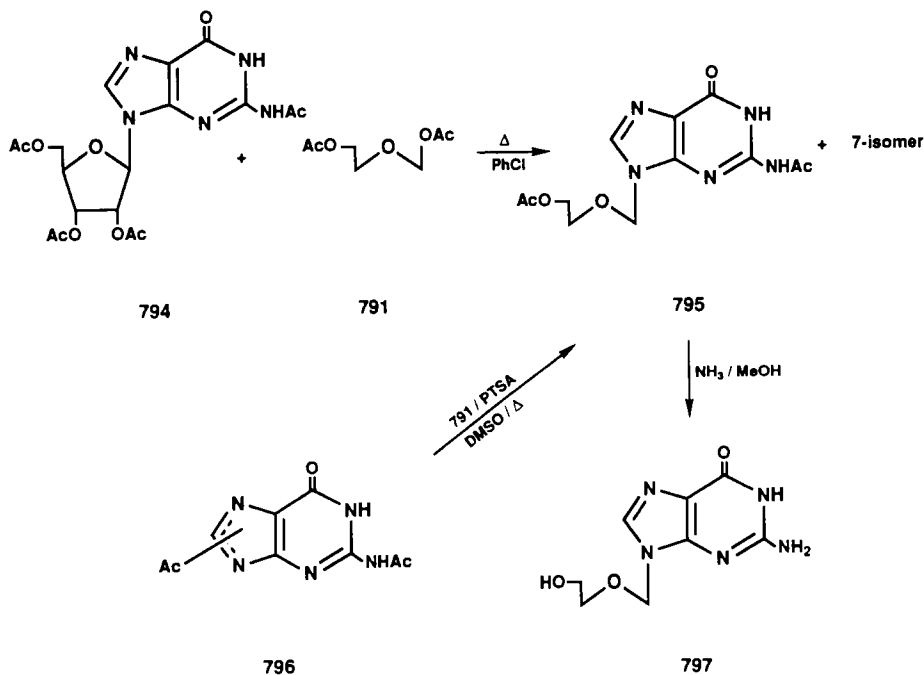
SCHEME 154



Coupling of the bis(trimethylsilyl) derivative of 5-benzyluracil **789** with 2-acetoxyethyl acetoxymethyl ether (**791**) in presence of  $\text{SnCl}_4$  was complex. In addition to the expected N-1 substituted product **790**, the N-3 substituted derivative **792** and disubstituted product **793** were also isolated. However, treatment of **789** with **783** in  $\text{CH}_3\text{CN}$  in the absence of  $\text{SnCl}_4$  gave **790** as the only isolated product. Deblocking of **790** with  $\text{NH}_3\text{-MeOH}$  gave the free nucleoside (88SC931).

A synthesis of acyclovir was achieved via a transglycosylation process by reaction of tetraacetylguanosine **794** with (2-acetoxyethyl)acetoxymethyl ether (**791**) using chlorobenzene as a solvent to give the respective 9-isomer **795** and its 7-isomeric analog. Heating the 7-isomer gave a mixture of both the 7- and 9-isomers (87MI5; 89MI9). Heating **796** with **791** in a solution of DMSO and in presence of PTSA also gave a mixture of the 9- and 7-isomers (86MI1). Treatment of the diacetate **795** with methanolic ammonia afforded acyclovir **797** whereas treatment with alkali effected selective *O*-deacetylation.

Deamination or dechlorination of the prodrugs of the 6-amino or 6-chloro moiety of 2-amino-6-substituted purines that are key intermediates



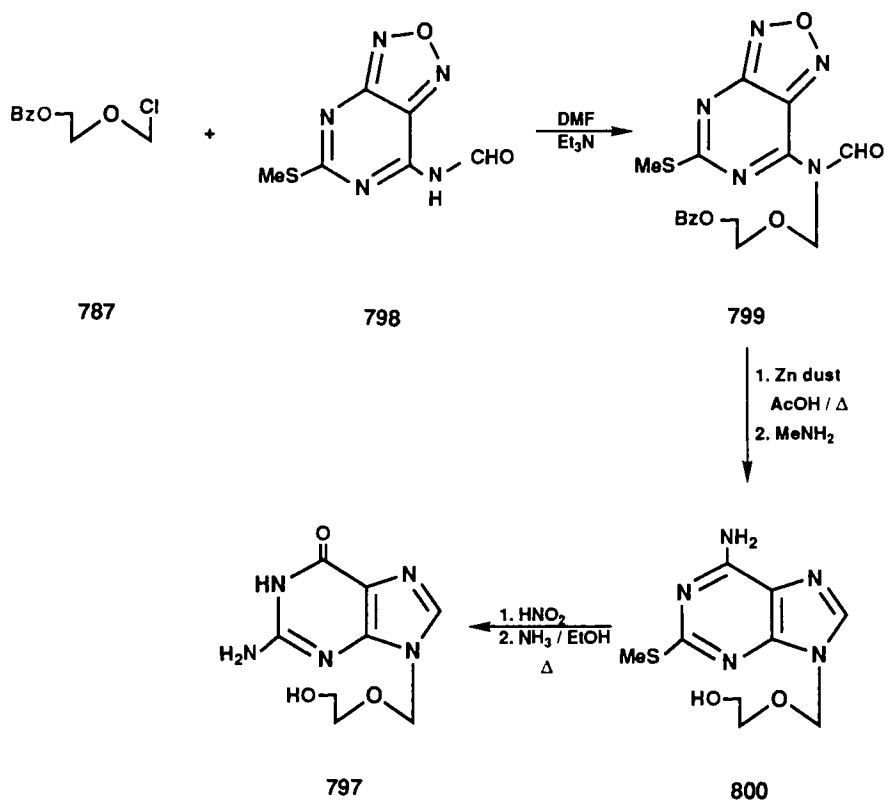
SCHEME 155

during the synthesis of ACV could be achieved with adenosine deaminase (82CJC547; 83MI1, 83MI3). Oxidation with xanthine oxidase of the 6-deoxyacyclovir, prepared as a water-soluble prodrug, gave acyclovir (84PNA3209).

## 2. Modifications on the Heterocyclic Rings

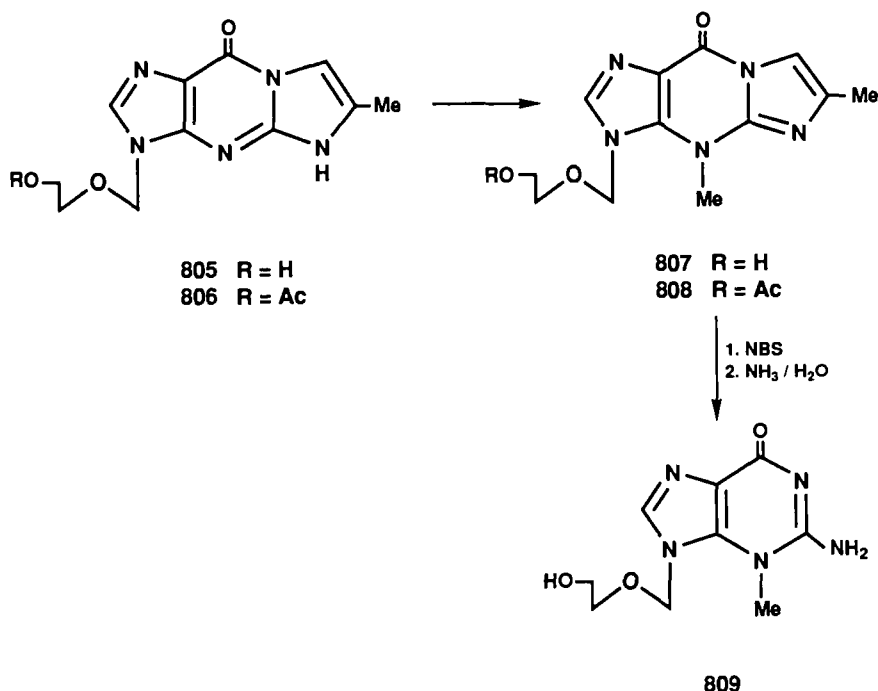
ACV was also prepared by coupling furazono[3,4-*d*]pyrimidine **798** with **787** to give **799**, followed by reductive cleavage of the furazan ring to give **800**. Hydrolysis of the 6-amino group followed by amination gave acyclovir (**797**) (86JHC271). Water-soluble, solution-stable, and biolabile *N*-substituted (aminomethyl)benzoate ester prodrugs of acyclovir were prepared (91MI7).

Coupling 2-(acetoxymethoxy)ethyl acetate **791** with **801** gave **802**, whose deacetylation gave **803** that on reaction with bromoacetone gave **804**. Ace-



SCHEME 156

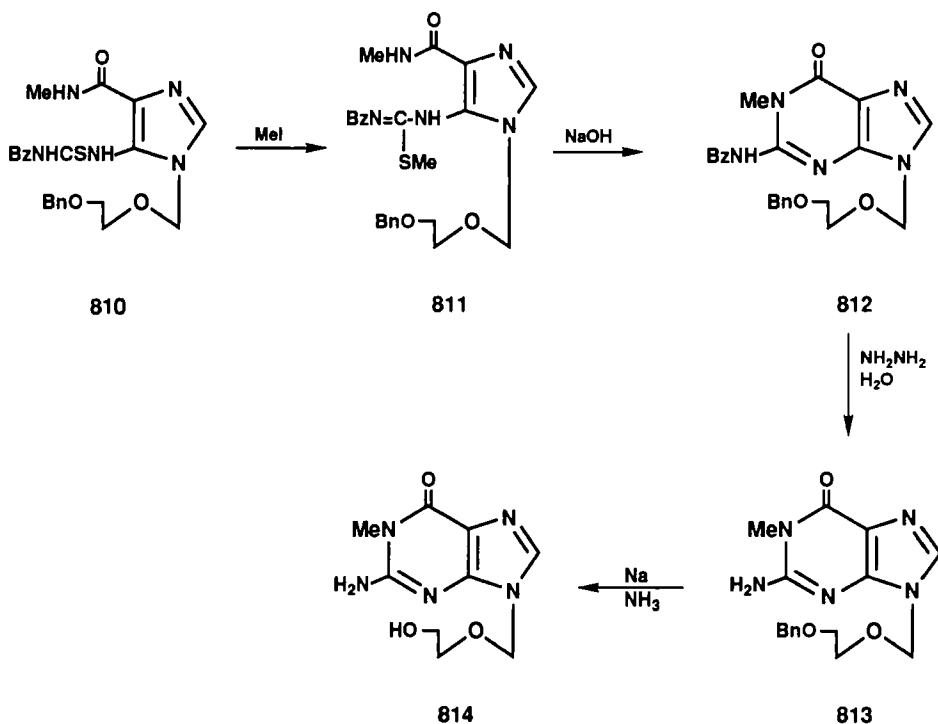




SCHEME 158

(90JHC1307). However, 1-alkylation was carried out by preparing the potassium salt in DMF using KOH powder, followed by addition of the alkylating agent, to give the 1-isomers **819**. Treatment with benzoyl isothiocyanate in acetone afforded **821**, which could be isolated or hydrolyzed *in situ* under mild conditions to the corresponding thioureas. Cyclodesulfurization could be done with a slight excess of the metal salt in aqueous sodium hydroxide. An excess of hydroxyl ions to compound **821** was found to be essential for the yield of the ring-closure reaction, the preferable ratio being 6 equiv hydroxyl ions to **821** to give **797** (90MI2; 91JOC2139).

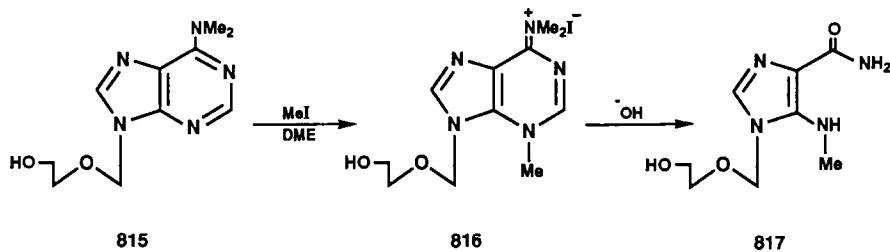
The synthesis of analogs in which the N-1 of acyclovir is replaced by an oxygen atom, as an acyclo analog of the antibiotic oxanosine, was achieved (89CPB229; 90JHC1307). Thus, treatment of **819** with alkali gave the respective sodium carboxylate that undergoes cyclization by acetic or propionic anhydride in pyridine to give **822** (90JHC1307). However, 4(5)-amino-5(4)-ethoxycarbonylimidazole coupled with 2-oxa-1,4-butanediol diacetate to give two positional isomers. Reaction of the 1-isomer with ethoxycarbonyl isothiocyanate followed by methylation at low temperature gave **827**, which could be cyclized with alkali to give **828** and **823** after neutralization. When



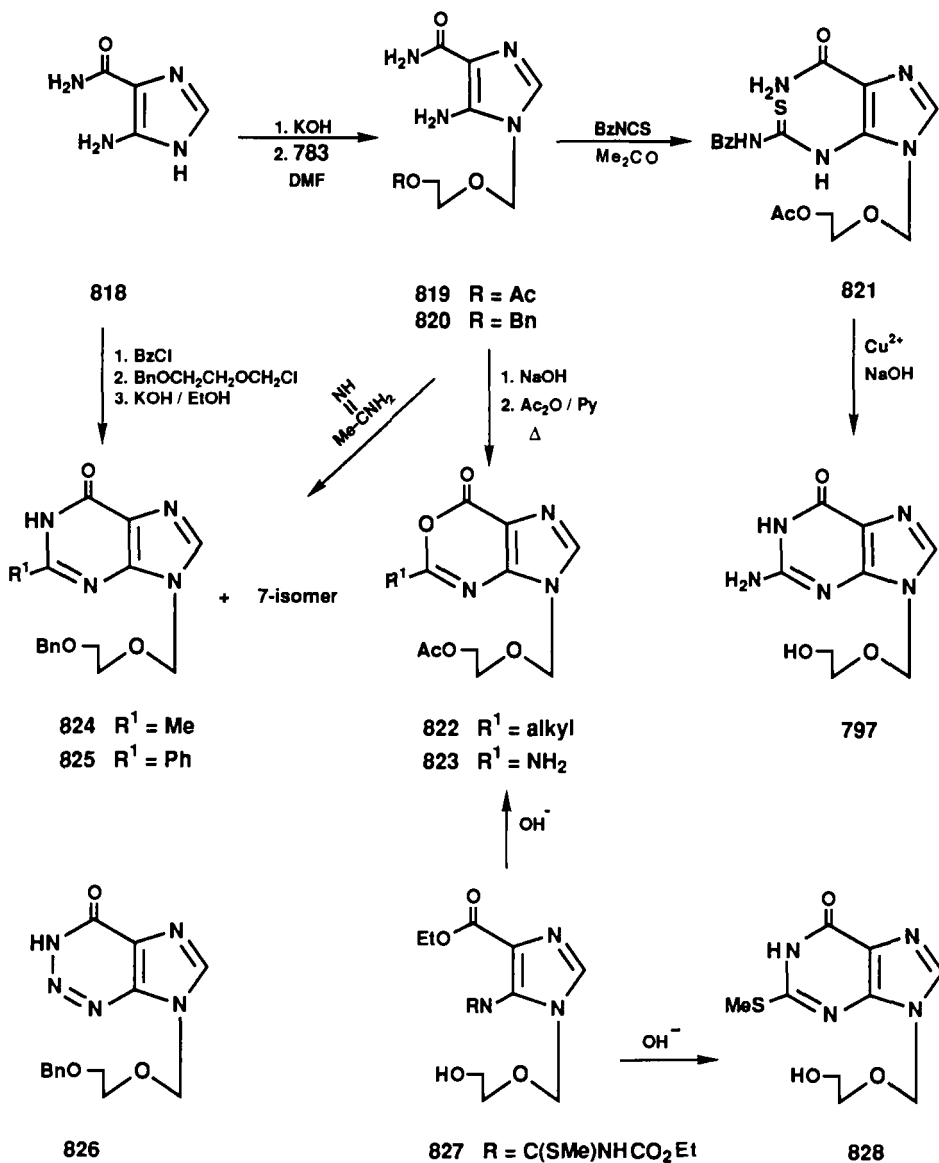
SCHEME 159

the methylation was carried at low temperature, the yield of **827** decreased because of the formation of **828** [89CPB229; 90JAP(K)02/091077]. The oxazine analog was found to be inactive to HSV-1.

Cyclization of **820** with acetamidine gave **824**. The phenyl analog **825** was prepared from **818** by benzylation to give the respective dibenzoyl derivative, whose alkylation gave the corresponding 9- and 7-alkylated



SCHEME 160



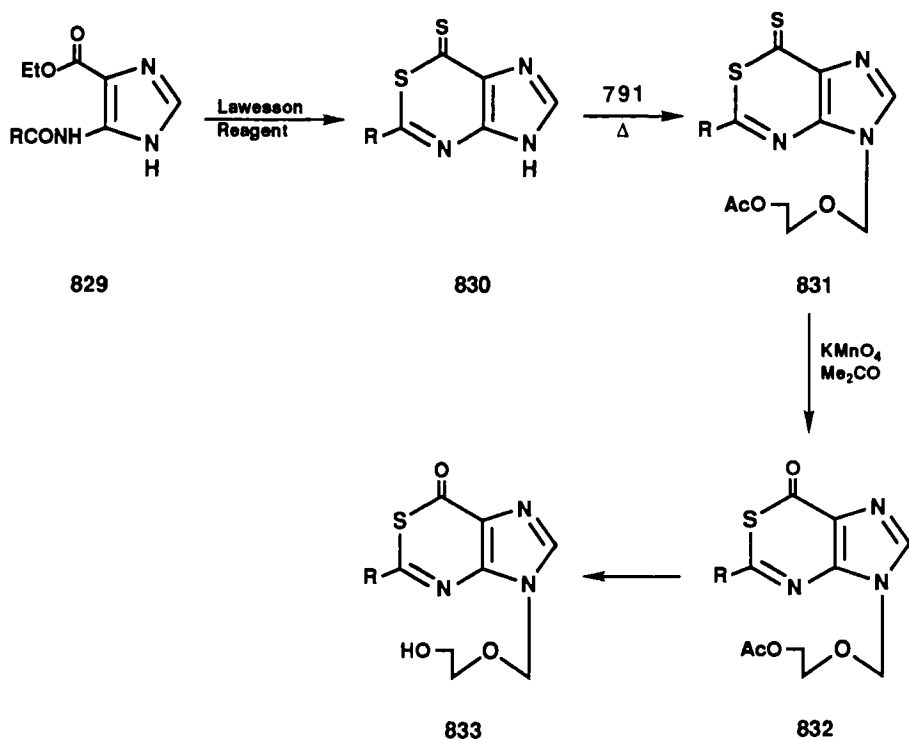
SCHEME 161

products. Further cyclization with alkali gave **825** and its 7-isomer (82JHC33). Cyclization of **820** with nitrous acid gave **826**.

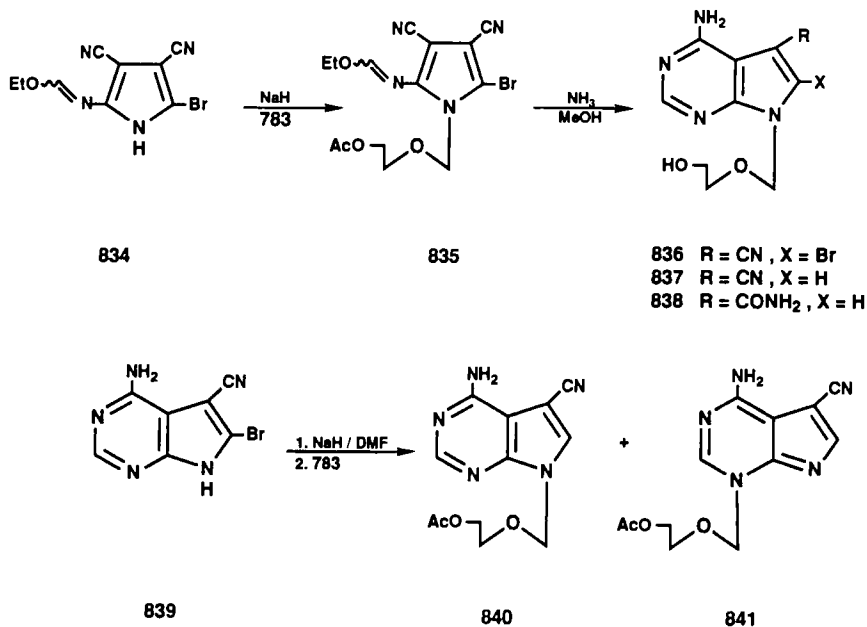
Thiazine compounds **830**, prepared from **829** by the Lawesson reagent, were converted to the corresponding (2-acetoxyethoxymethyl)imidazothia-

zine derivatives **381** by fusion with 2-oxa-1,4-butanediol diacetate in absence of a catalyst. The 5-phenyl derivative gave a mixture of positional isomers, whereas other derivatives gave 3-substituted derivatives as the only isolable products. The alkylation of some derivatives was carried out via the silyl derivative of **829**. Replacement of the S with O gave **832**, whose deacetylation gave **833** [89NAR128; 91CPB871; 93JAP(K)05/163282]. It is worth mentioning that coupling of the mercury chloride salt of 4-methyl-5-nitroimidazole with **783** gave a mixture of the respective 3-isomer and the 1-isomer, which bears a 2-acetoxyethyl group rather than an acetoxyethoxymethyl group (86MI1).

Coupling of **834** with **783** gave **835**, which cyclized to **836** (92MI8). However, treatment of the sodium salt of **839** with **783** afforded a mixture of two major positional isomers of nucleosides. The reaction is thermodynamically controlled. At room temperature the N-1 isomer predominates, whereas formation of the N-7 isomer increases with an increase in temperature. Debromination of the mixture gave **840** and **841**, which could be separated.



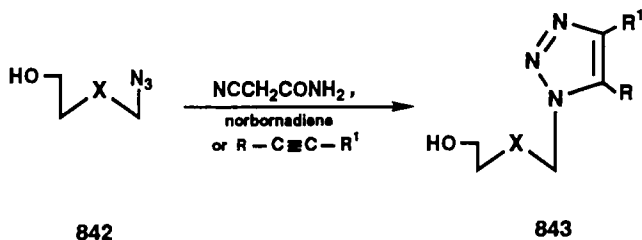
SCHEME 162



SCHEME 163

Deacetylation of **840** gave **837**. The nitrile group in **837** could be transformed into other functional groups such as **838** (89JMC1420; 90JMC2162). None of these compounds caused significant inhibition of cell growth. Only the corresponding thioamide was active against human cytomegalovirus (HCMV) and HSV-1. The 3-cyano-3-deazaguanine analog is more potent against GPCMV replication when compared to parental drugs DHPG and ACV (91MI3).

1,2,3-Triazole and 8-azapurine derivatives **843** were prepared by the cyclocondensation of the acyclic azide derivative **842** with cyanoacetamide, norbornadiene, and acetylene derivatives (90H1669).



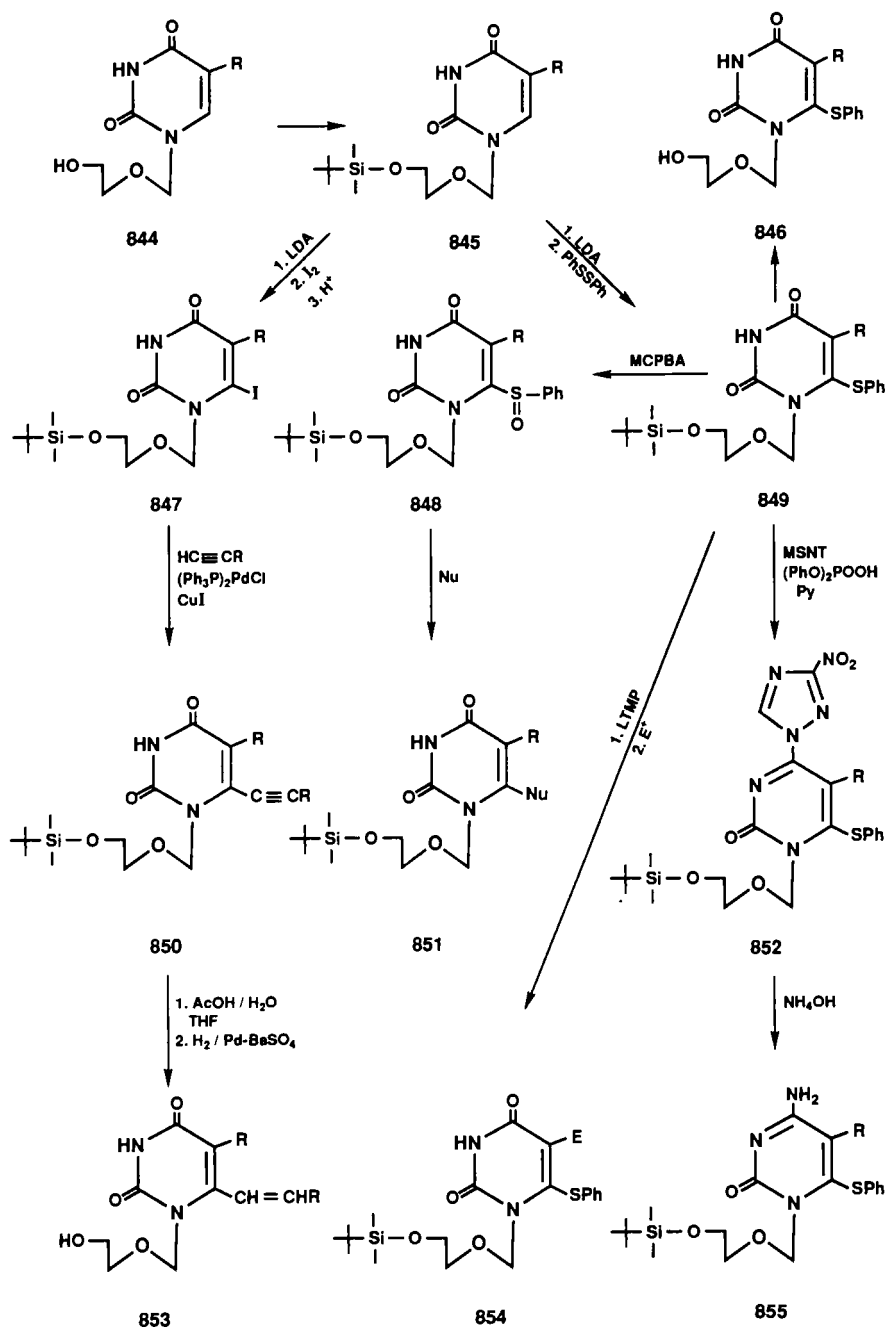
SCHEME 164



### 3. HEPT Analogs

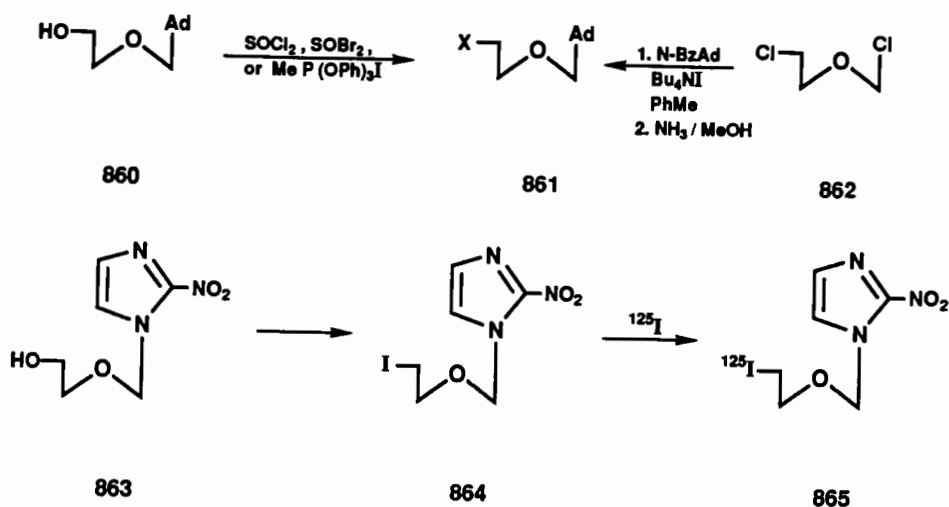
1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine, abbreviated as HEPT, has potential biological activity that led to its consideration as a lead compound. It was prepared by lithiation at the C-6 position followed by conversion to the 6-phenylthio derivative. Lithiation of nucleosides has demonstrated that this strategy offers a general entry for modifying the base moiety. When lithium diisopropylamide (LDA) is used as a lithiating agent, regiospecific abstraction of the more acidic proton H-6 of uridine analogs can be achieved. This provides various types of 6-substituted derivatives (91JMC349; 92JMC337). Thus, silylation of **844** gave the protected nucleosides **845**, which were lithiated with LDA, and the C-6 lithiated species was heated with diphenyl disulfide or iodine to give the 6-substituted derivatives **849** and **847**, respectively. Upon desilylation, the desired 6-substituted acyclonucleosides were produced. The structure of **846** was confirmed by X-ray crystallography (89JMC2507). Analogs having selenium instead of sulfur were synthesized (91JMC3305). The 5-ethyl HEPT analogs were also synthesized (91MI9). Significant antileukemic activity was observed in a series of HEPT and 6-iodouridines. HEPT was found to show an inhibitory effect on the cytopathogenicity of HIV-1 in MT-4 cells (91MI4), and it can be considered as a highly specific lead for an anti-HIV-1 agent (91MI11).

Lithiation of the C-5 position was carried out with LTMP and when followed by electrophilic reactions gave **854** (90NAR127). Oxidation of **849** with MCPBA gave the respective 6-phenylsulfinyl derivative **848**, whose reaction with nucleophiles gave compounds **851** having oxygen- and nitrogen-containing substituents at the C-6 position (91JMC349). The 6-iodo analog **847** could be converted to **850** and **853**. Analogs of **846** having substituents on the phenylthio ring were also synthesized (91MI13; 92JMC337). The 4-amino analog **855** was synthesized by starting with **849**, conversion to the 4-(3-nitro-1,2,4-triazolyl) intermediates **852** by reaction with 1-(mesitylene-2-sulfonyl)-3-nitro-1,2,4-triazole in the presence of diphenyl phosphate followed by treatment with ammonia (91JMC1394). The 4-thio analogs were prepared by lithiation of the 4-*O*-benzoyl derivatives with Lawesson's reagent (91JMC1394). The 2-thio analogs were prepared by the C-6 lithiation methods. Methylation and benzylation of the N-3 portion were carried out. A variety of HEPT analogs were synthesized; the hydroxyl group of the acyclic portion was altered to deoxy, deoxy halogeno or azido groups, ether, or ester groups, so they could not be phosphorylated (91JMC1508). Other acyclic analogs were also prepared (92MI7).



SCHEME 165

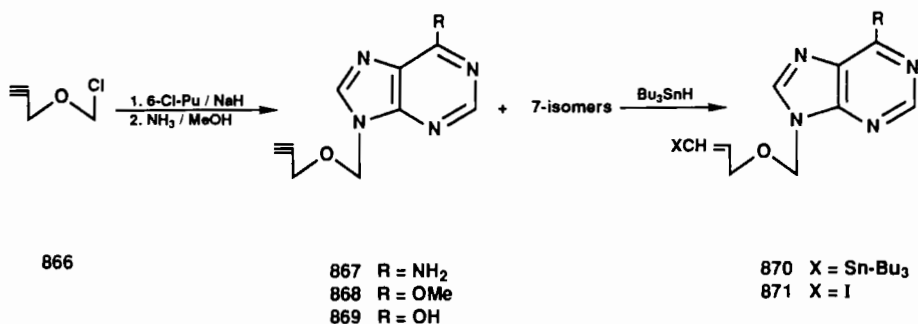
**SCHEME 166**



SCHEME 167

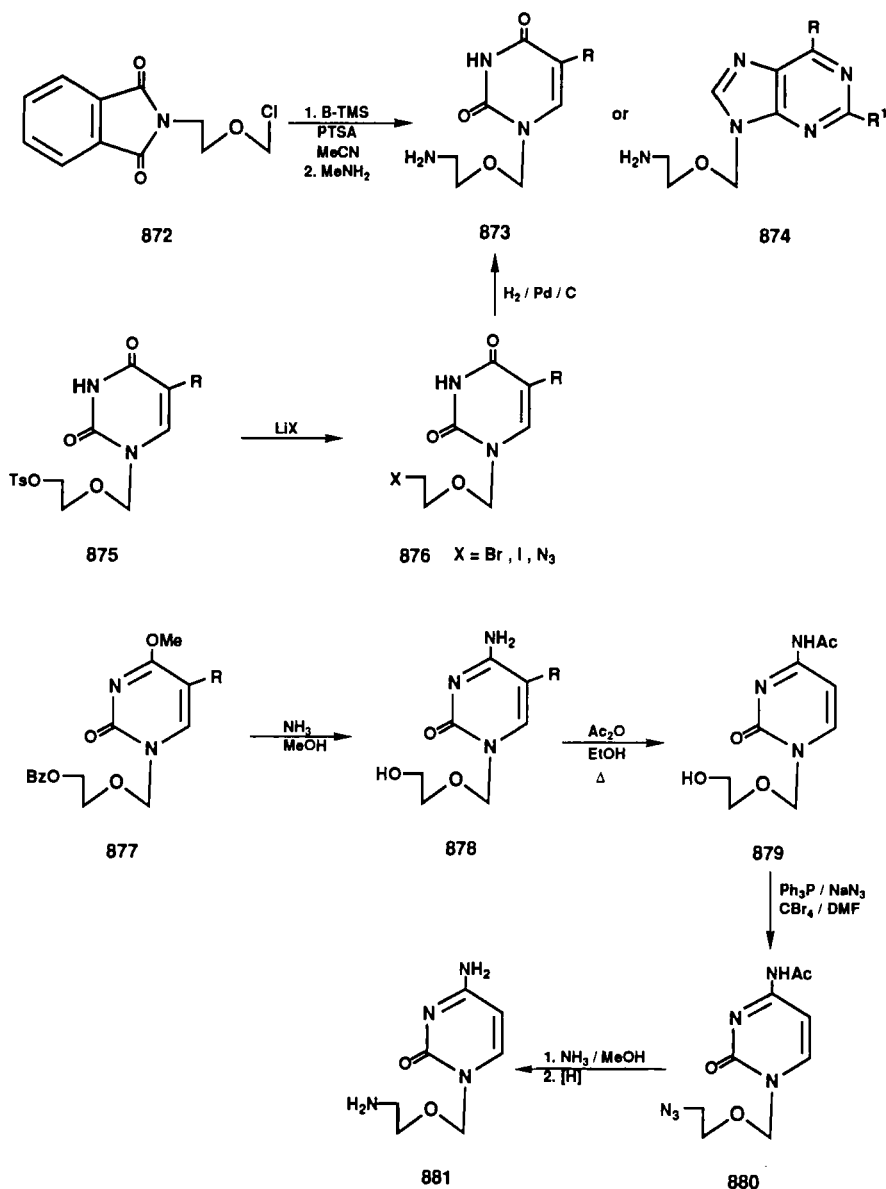
yield, but it was conveniently prepared from the diazotization of **867**. Hydro-metalation of **867** or **869** with tributylstannyl hydride in presence of azobis (2-methylpropionate), with subsequent iododestannylation of **870** with sodium iodide, gave angustycin A analog **871** as the Z isomer. The  $^{125}\text{I}$  radiolabeled analogs were useful as potential metabolic markers. The 6-thio analog of **869** was also prepared. The unsaturated nucleosides showed inhibition of cancer cell growth.

Phthaloylation of 2-aminoethanol followed by chloromethylation gave **872**, which coupled with the silylated 5-substituted uracils, 6-dimethylami-



SCHEME 168

nopurines or guanine. The diaminopurine analogs were made via the sodium salt. Deprotection by methylamine or hydrazine gave the respective nucleosides **873** and **874** (81JMC472, 81JMC1528; 85JPS1302).



SCHEME 169

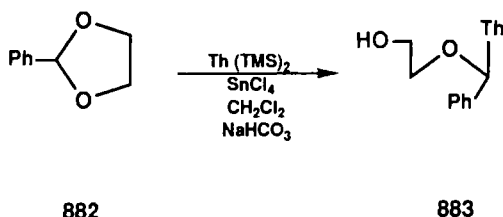
Alternatively, displacement of the tosyloxy group in **875** with lithium halides or azides gave **876**, whose reduction with  $\text{H}_2/\text{Pd/C}$  gave **873** (81JHC947; 87HCA219). Similarly, displacement of the bromo atom by azide was used for the preparation of the cytosine analog **881**. Thus, debenzoylation of **877** accompanied by amination to give **878**. Selective acetylation of **878** gave **879**, which converted to the azido derivative **880**; deacetylation and catalytic hydrogenation gave **881** (81JMC1078). The carbamoyl derivative of **878** was prepared by treating **879** with phenyl chloroformate in pyridine and methylene chloride followed by treatment with ammonium hydroxide. The prepared nucleosides were inactive against leukemia L-1210 cells in culture. However, a number of them inhibited the *in vitro* growth of *E. coli* K-12; the most potent among these was 1-[(2-hydroxyethoxy)methyl]-5-fluorouracil. None of the cytosine derivatives tested served as either substrates or inhibitors of human liver cytosine nucleoside deaminase.

Acyclonucleosides having a phenyl substituent on the C-1' position as in **883** was prepared by condensation of the dioxolane **882** with bis(trimethylsilyl)thymine in presence of  $\text{SnCl}_4$  (90GEP3906357).

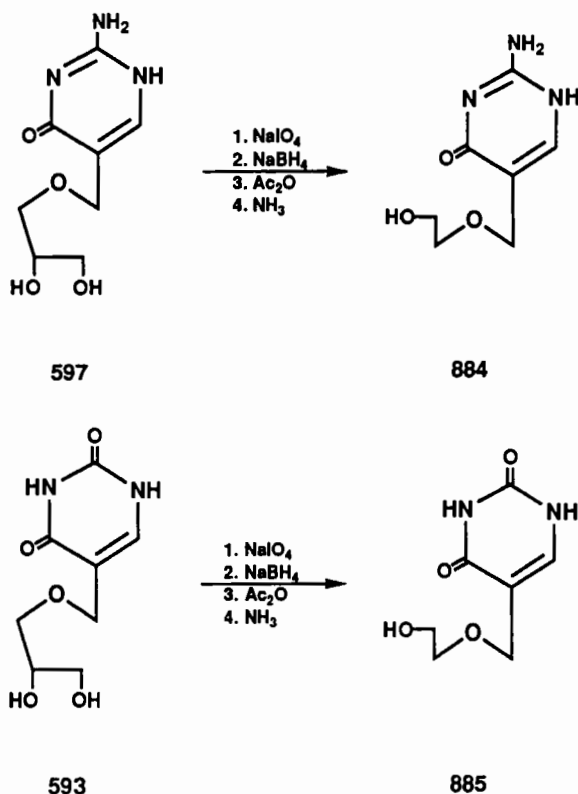
### 5. *Acyclo-C-nucleoside Analogs*

The C-nucleoside analogs were prepared by periodate oxidation of **597** and **593**, followed by reduction and purification by acetylation, followed by deacetylation to give **884** and **885**, respectively (86JHC1621).

Acyclopseudouridine **885** and acyclopseudoisocytidine and their 1-methyl derivatives were synthesized from 5-(hydroxymethyl)uracil (**592**) or by an inferior method from the 5-(chloromethyl)uracil (**886**) by reaction with ethylene glycol (**887**) (83MI4; 84JHC9). The pyridine analog **888** was similarly prepared from **416** (91T10065). Methylation of **885** with DMFDMA gave a dimethyl derivatives **889** ( $\text{R} = \text{Me}$ ) and methylation with  $\text{MeI}$  in HMDS gave a monomethyl derivative **889** ( $\text{R} = \text{H}$ ). The ring transformation of the uracil derivative **889** to the isocytosine derivative **884** was accomplished with free guanidine. Selective methylation of **884** gave



SCHEME 170



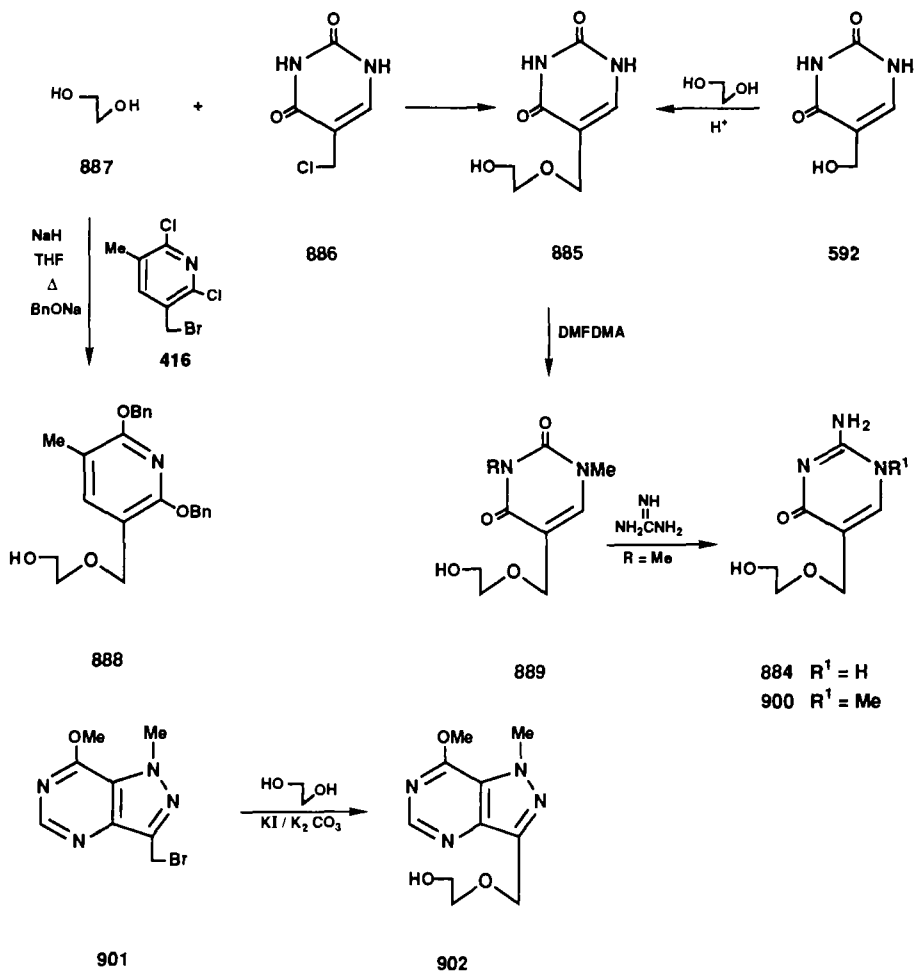
SCHEME 171

**900.** The formycin analog **902** was prepared from **901** (84JHC505). It was inactive against HSV-1 and HSV-2.

The C-nucleoside analog **907** was prepared from **903** by hydrolysis to the amide **904** followed by condensation with the diamine **905** to give **906**, which underwent dehydrative cyclization to **907** (83JHC1169).

The thioimide **908** is an excellent precursor for building heterocyclic rings. Thus, it underwent cyclization with aminocyanoacetamide to give **909**, which cyclized to **910**. However, reaction of the thioimide **908** with the hydrazine **911** or **912** gave **913**, whose reduction and deprotection gave **914**. A Dimroth rearrangement had taken place during the last cyclization (83JHC1169). Similarly, the cyclization of **908** with 5-benzyloxy-4-hydrazinopyrimidine gave 2-(2-benzyloxyethoxymethyl)-8-benzyloxy-1,2,4-triazolo[1,5-c]pyrimidine (89JHC991).

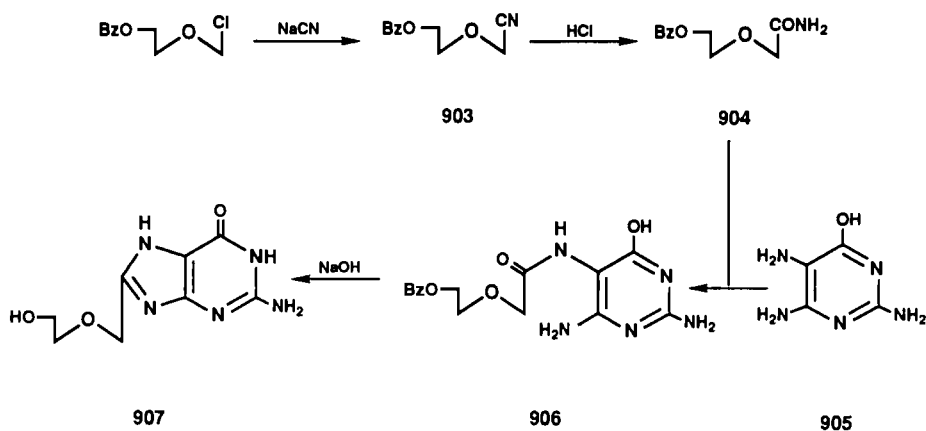
The precursors for building the heterocyclic rings in the C-nucleoside isosters **923** were **917** and **920**. The former was prepared from ethyl bromo-



SCHEME 172

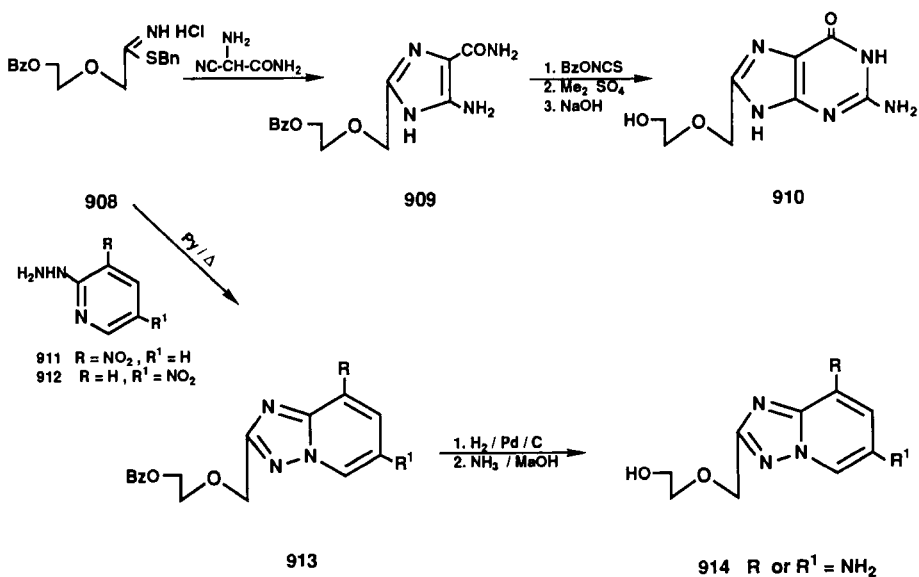
pyruvate by reaction with dibenzylamine to give the unstable derivative **915**, whose cyclization with aminoguanidine gave **916**, which deprotected to give **917**. The hydrazine **920** was prepared from **918** via **919**. The C-nucleosides were then prepared by dehydrative coupling of the acid **921** with **917** or **920** using *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) to give **922**, whose cyclization with  $\text{POCl}_3$  followed by a subsequent debenzoylation gave **923** (84JHC697). They showed no activity against HSV-1 and HSV-2.



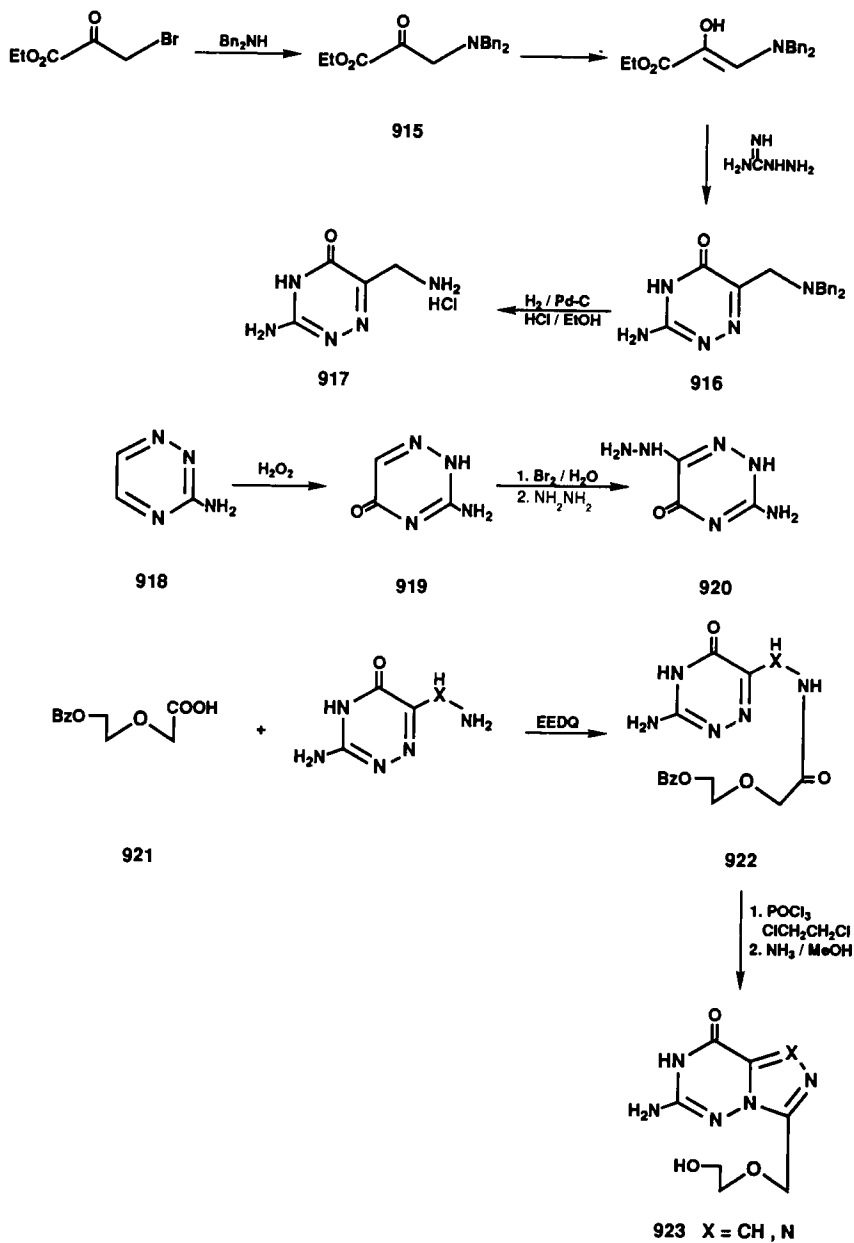


SCHEME 173

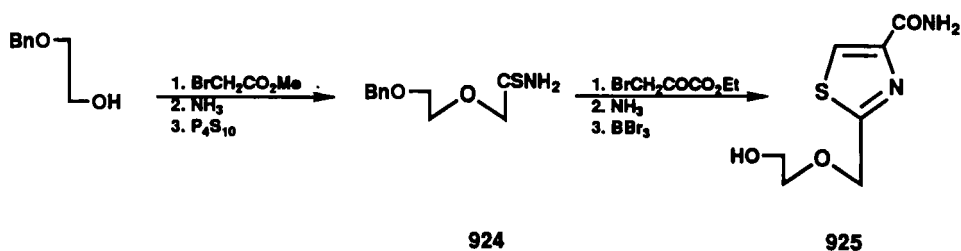
The thiazofurin acyclic analog **925** was prepared from **924** as shown in the scheme (87H947). 1,3-Dipolar cycloaddition of the acetylenic derivative **927** to the diazo derivative **926** gave the pyrazole **928**, whose amidation and debenzoylation gave **929** (93MI11).



SCHEME 174



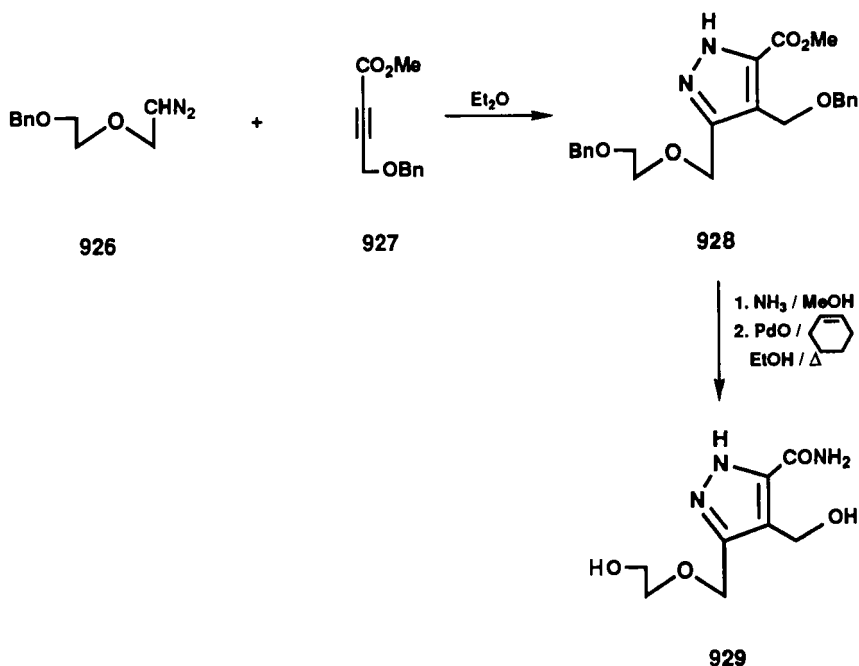
SCHEME 175



SCHEME 176

### 6. Carboacyclic Analogs

The carboacyclic nucleoside analogs considered under this section could be also considered in Section III,G as a component resulting from two bond disconnections. However, it is preferable to consider them as acyclovir analogs. The carboacyclonucleosides having purine **934** and 8-azapurine rings **935** have been prepared starting by reaction of 2-amino-

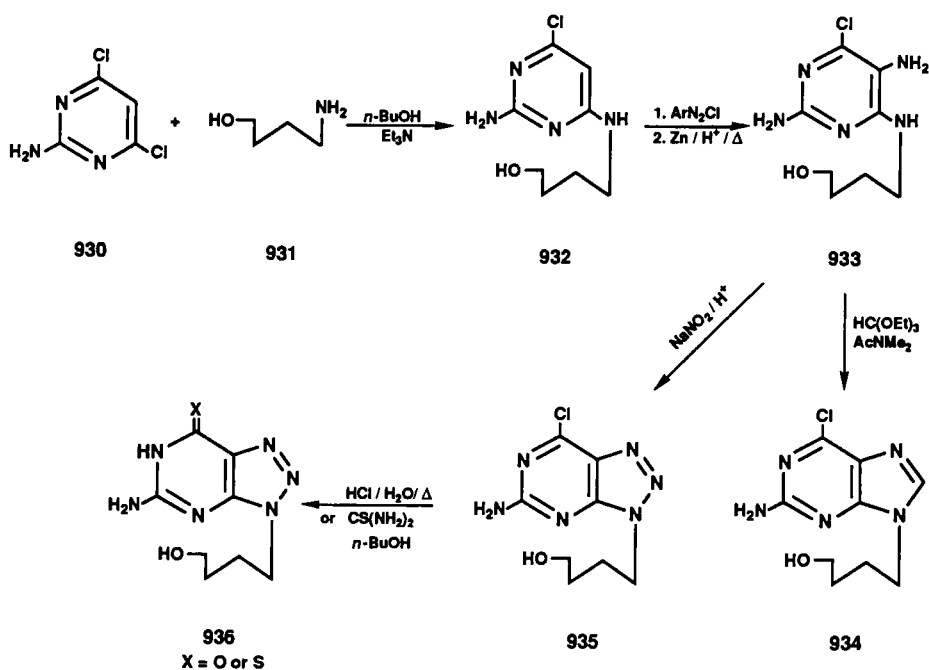


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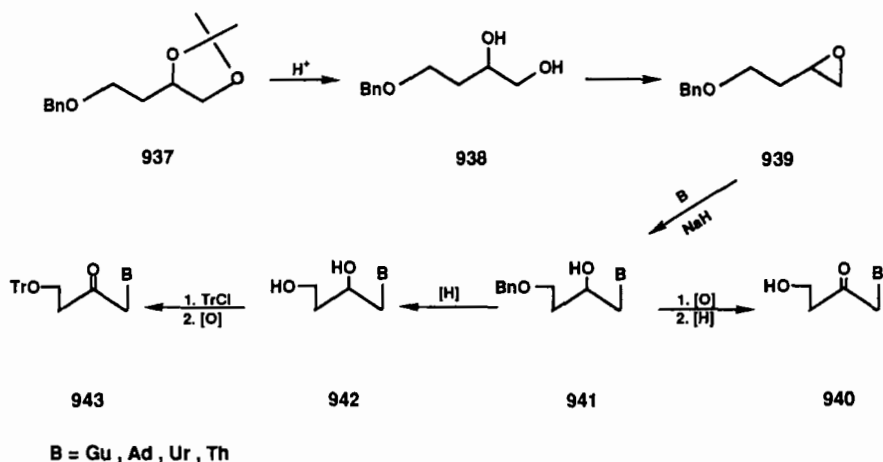
4,6-dichloropyrimidine **930** and 4-amino-1-butanol **931** to give **932**. Its reaction with a diazonium salt followed by reduction gave **933**, which upon cyclization with triethyl orthoformate gave **934** and with nitrous acid gave **935**. Hydrolysis of the latter with acid gave **936** ( $X = O$ ), whereas its treatment with thiourea gave the thio analog **936** ( $X = S$ ) (90JHC1409).

The carbacyclic analog of acyclovir is 9-(4-hydroxybutyl)guanine (HBG), whose crystal structure was determined (87MI7). The side chain is fully extended and almost perpendicular to the guanine base.

The precursor for the synthesis of 2'-oxocarboacyclic analogs was **939**, which was prepared from **937** by deisopropylidenation to **938** followed by conversion to the epoxide **939**. The key condensation reaction was the treatment of electrophile **939** with an excess of the bases guanine, adenine, uracil, or thymine and a catalytic amount of sodium hydride to give adducts **941**. Hydrogenolysis of **941** afforded the 2,4-dihydroxybutyl derivatives **942**. Conversion of **941** to ketones **940** was carried out by Moffatt oxidation and then hydrogenolysis. In the purine series, **942** were first tritylated and then oxidized to give **943**, which in turn were hydrolyzed to furnish **940**. The  $N^2$ -trityl protecting group was found to greatly improve the yield of the Moffatt oxidation of the guanosine derivative. Acyclic guanosine analog



SCHEME 178

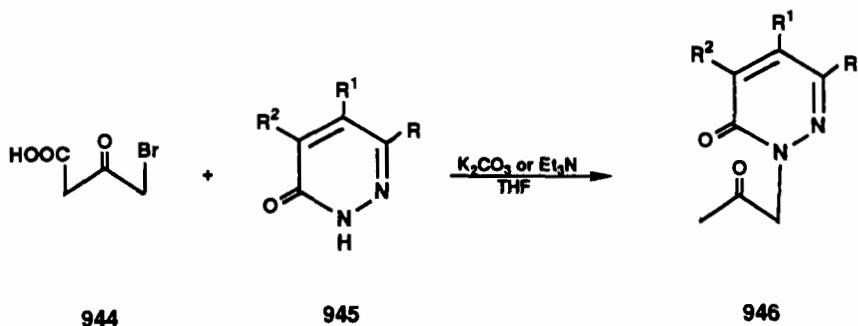


SCHEME 179

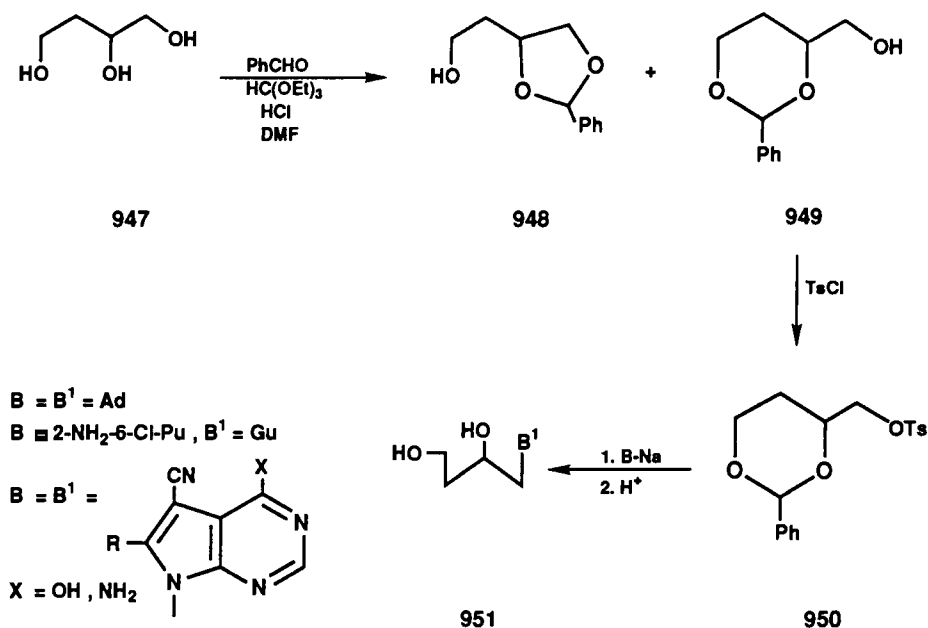
**940** was a substrate for, but did not irreversibly deactivate, the herpes virus-specific enzyme thymidine kinase (85JOC755).

Alkylation of pyridazinone **945** with 4-bromoacetoacetic acid **944** did not give the 2'-oxo-4'-carboxylic acid analogs, but gave **946** of type 4.1. The uracil derivatives were prepared similarly (90MI4).

The 2'-hydroxy analog of acyclovir **951** were also prepared. The synthesis commenced with 1,2,4-butanetriol **947** whose benzyldienation gave **949** and a small amount of **948**. *p*-Toluenesulfonylation of the mixture gave **950** as a crystalline product, which alkylates the alkali metal salts of adenine or 2-amino-6-chloropurine in the presence of  $\text{K}_2\text{CO}_3$  in DMSO to give the 9-alkylated isomer and a small amount of the 7-alkylated product. Subsequent acid-catalyzed hydrolysis gave **951** (84MI2; 90JMC2162). Little or no activity was shown in antiviral assays with several DNA and RNA viruses.



SCHEME 180



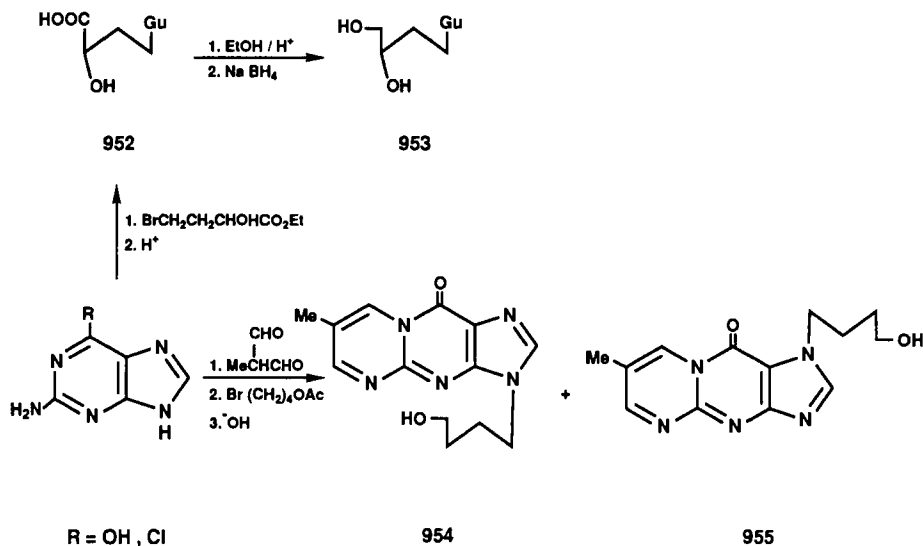
SCHEME 181

The 3'-hydroxycarboacyclic analog **953** was prepared by alkylation of the 2-amino-6-chloropurine with ethyl-4-bromo-2-hydroxybutyrate, followed by hydrolysis to give **952**, whose esterification and reduction gave **953**, which inhibited herpes simplex type 1 plaque on vero cell monolayers [86ACSA(B)310]. Direct alkylation of the condensed heterocycle resulting from the cyclization of guanine with methyl malonoaldehyde followed by deacetylation gave **954** and **955**.

The fluorinated carboacyclic analogs **958** were prepared by coupling the triflylate of the fluorinated carbon-chain backbone **956** with bases to give **957**, whose deprotection gave **958** (91TL3823). They were less active than acyclovir.

The branched carboacyclic analogs of the type **961** were prepared from a purine derivative and a haloalkylidene malonate **959** to give **960**, which was hydrogenated to give **961** (91EUP420559).

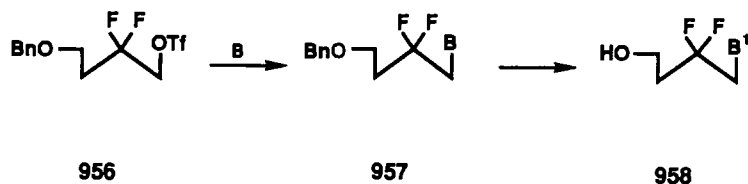
A series of purine acyclonucleosides with guanine and a four-carbon chain having a 2'-substituent (F, NH<sub>2</sub>, N<sub>3</sub>) and 3',4'-dihydroxy had been evaluated as inhibitors of mammalian purine nucleoside phosphorylase (91MI8).



SCHEME 182

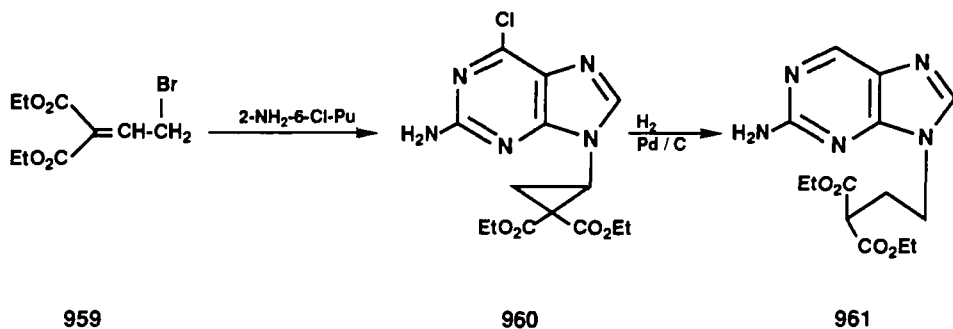
The synthesis of **964** was achieved by coupling 6-chloropurine and 4-methylthiobutan-1-ol (**962**) under the influence of DEAD/Ph<sub>3</sub>P to give **963**, followed by ammonolysis to **964** [93JCS(P1)1109]. It was a potent inhibitor of the enzyme methylthioadenosine nucleosidase.

More rigid analogs may have superior biological activity as a consequence of the constraint that is imposed on side-chain flexibility. This may be achieved by the internal incorporation of unsaturation or a cyclopropane ring. Such analogs can be considered to be analogs of acyclovir rather than analogs of type 2.7. Thus carboacyclic analogs having a double bond in the alkyl side chain were prepared as acyclic analogs of neplanocin. Neplanocins



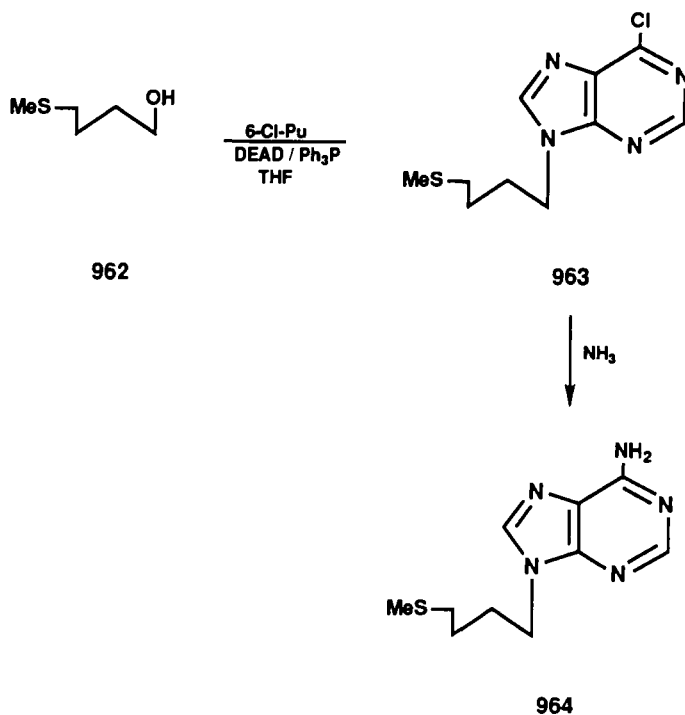
B = 2-NH<sub>2</sub>-6-Cl-Pu, N-Ac-Cy ; B<sup>1</sup> = Gu, Cy

SCHEME 183



SCHEME 184

are a group of carboacyclic nucleosides in which the ribose moiety is replaced by a cyclopentene ring; one of them, neplanocin A, is a more potent antitumor agent than other drugs. The acyclic analogs **966** were prepared by condensation of the base with the *trans*-dichloride **965**, followed

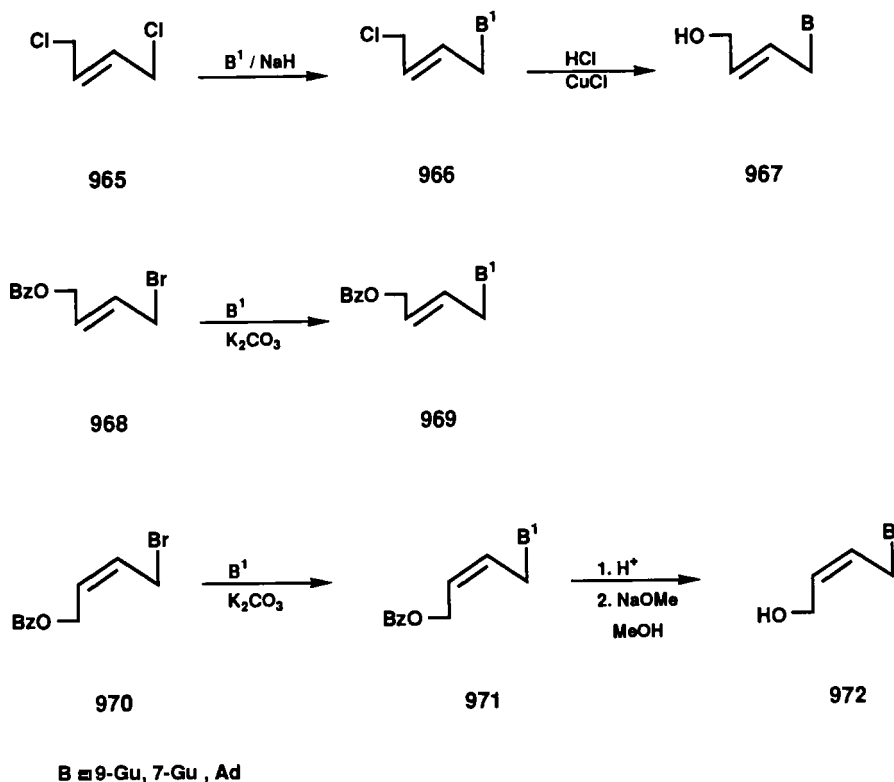


SCHEME 185

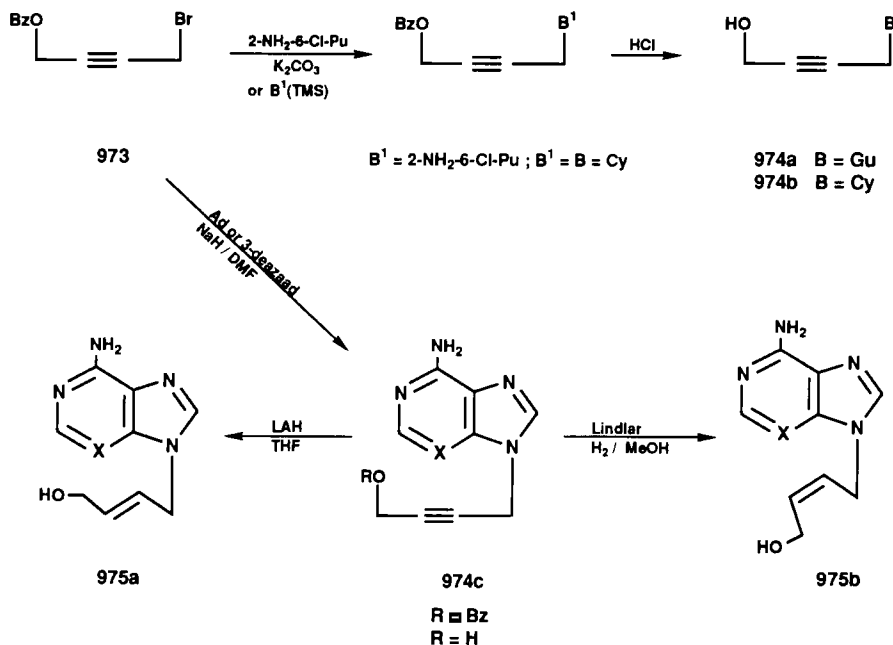


by hydrolysis with alkali or HCl to give **967**. The alkylation could be affected by NaH in DMF (87JMC198),  $K_2CO_3$  in DMSO or TBAF in THF (87JMC437; 89MI11; 91JMC421). Alternatively, **967** could be prepared from the bromoalkenylbenzoate **968** by coupling to give **969**, followed by hydrolysis (88JMC2304). The *cis*-analog **972** was prepared from the alkylation of 2-amino-6-chloropurine with **970** to give **971** followed by acid hydrolysis and then debenzoylation. The adenine derivative was directly debenzoylated. The adenine analog **967** exhibited significant cytotoxicity against P-388 mouse lymphoid leukemia cells and the guanine analog of **972** inhibited replication of herpes simplex viruses type 1 and 2.

The corresponding acetylenic analogs **974a** or **974b** were prepared from **973** by coupling and then hydrolysis (88JMC2304, 88MI2; 91JMC421, 91MI6). The acetylenic analogs could be isomerized to allenic nucleosides. However, these are considered in Sections IV,D or III,G. Reduction of



SCHEME 186



SCHEME 187

**974c** gave the *trans* **975a** or the *cis* **975b** olefinic analog, depending on the reducing agent (88JMC1729).

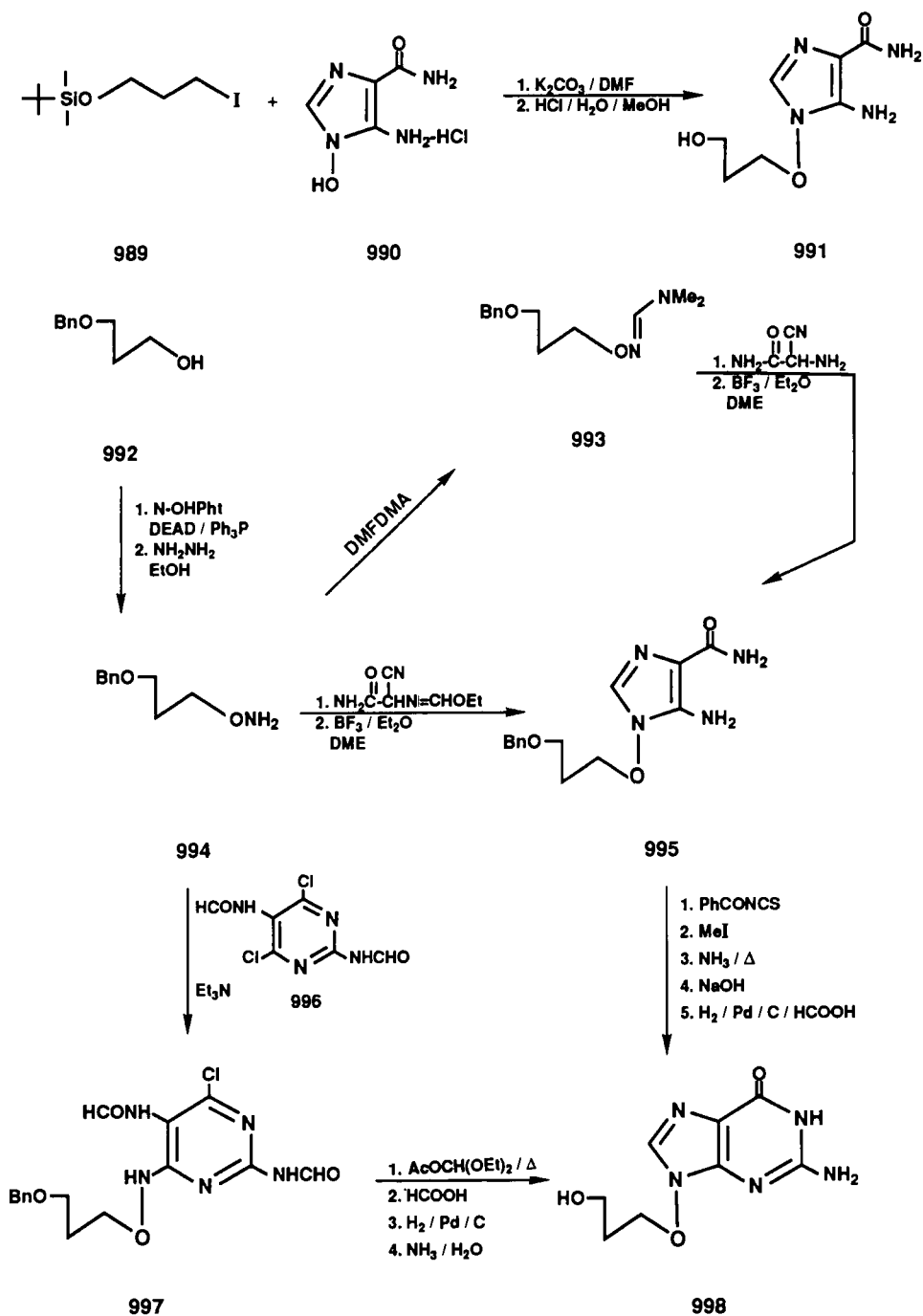
The cyclopropyl analogs were made from the aminoalcohol **977**, prepared from **976** by reaction with 6-chloroisocytosine followed by nitrosation to give the 5-nitroso derivative, which upon reduction in the presence of formic acid gave **979** as a mixture with its formyl derivative **978**. Ring closure of **978** gave **981**. When the catalytic hydrogenation was done in acetic acid, **979** was obtained; further cyclization with nitrous acid gave **984**. Cyclization of **980** with chloroacetaldehyde gave **985** (88JMC2304). Alternatively, coupling the base with chloro derivative **982** gave acyclonucleoside **983**.

The carboacyclic *C*-nucleosides **988** were prepared by the cycloaddition of **987** with oxazinone **986** (91T10065).

### 7. Translocation of the Oxygen with Carbon Analogs

Translocation of the oxygen with C-1' of acyclovir gave analogs of potent biological activity. Their synthesis was achieved by two main methods. The first includes alkylation of the hydroxyimidazole derivative **990** with 3-



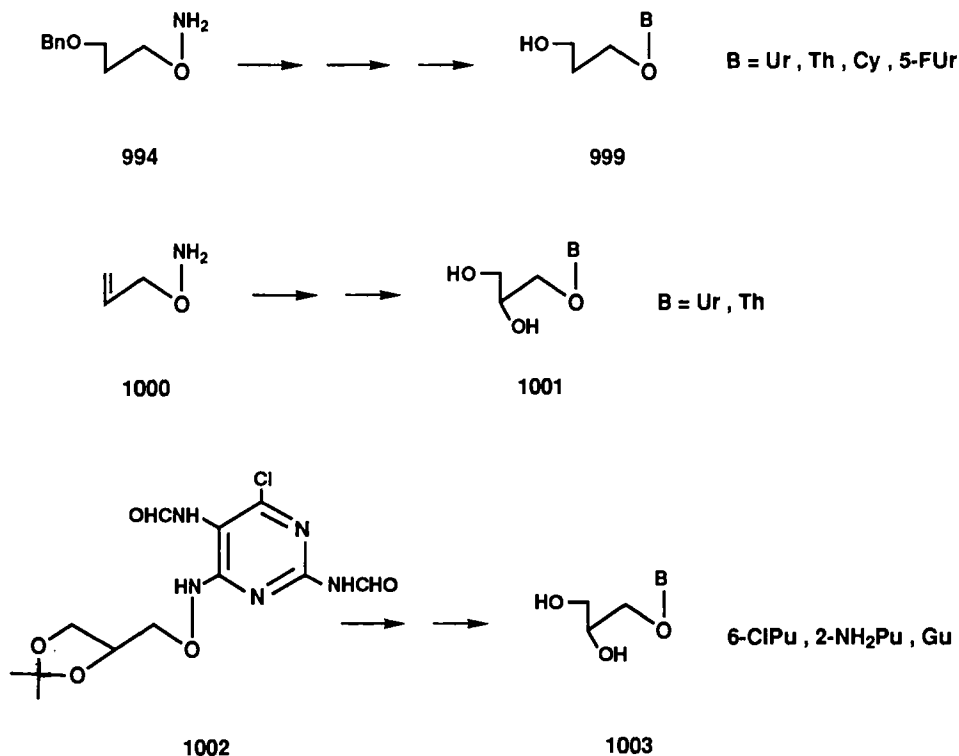


SCHEME 190

tertbutyldimethylsilyloxy-1-iodopropane **989**, followed by deprotection to give the nucleoside analog **991** (90S893).

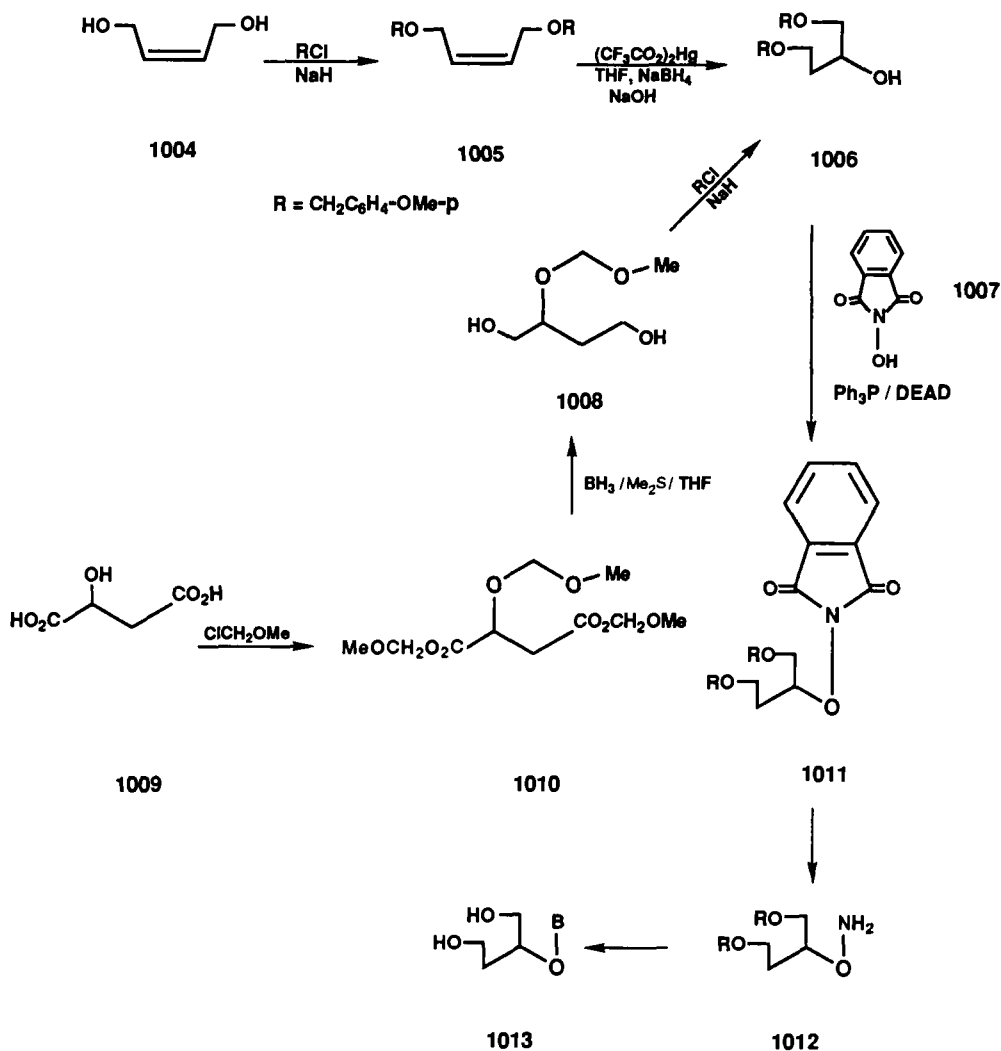
The 9-alkoxyguanines were efficiently prepared from the formylated pyrimidine **996** by reaction with the hydroxylamine derivative **994** to give **997**. Then, the imidazo ring was constructed and the product was deprotected to give **998** (88TL701). An efficient route to **998** started with imidazole **995**, then constructing the pyrimidine ring and then deprotection. The imidazole ring of **995** could be prepared from the hydroxylamine **994** by conversion to **995**, or alternatively from **992** by conversion to **993** and then to **995**.

Conversion of the amino group in **994** was achieved as before to give **999** [88TL4013; 90JCS(P1)2175; 91JMC57]. The hydroxy derivative **1001** could be obtained in a similar manner from **1000** with an extra hydroxylation step. The synthesis of the corresponding *R*- and *S*-enantiomers of 2,3-dihydroxypropoxy acyclonucleoside **1003** commenced from the enantio-



SCHEME 191

mers of isopropylidene glycerol by reaction with *N*-hydroxyphthalimide followed by hydrazinolysis and then reaction with **996** to give **1002**, followed by cyclization and then treatment with ammonia to give the purine. Conversion to the guanine was accomplished by reaction with formic acid and then ammonia. Treatment with ammonia gave 2-amino-6-chloropurine. Deisopropylidenation gave **1003**. Further dechlorination gave the 2-amino-purine (91JMC57).

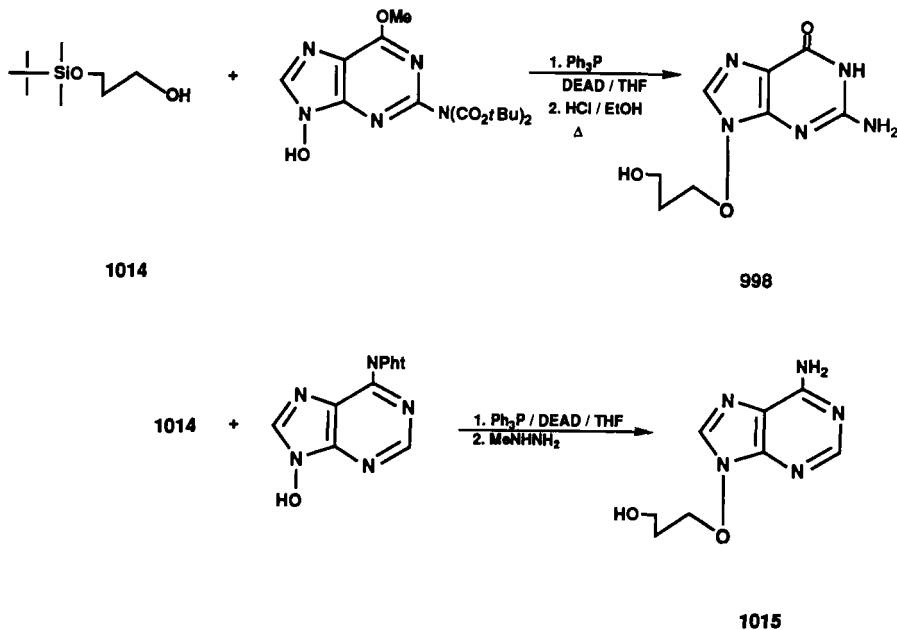


SCHEME 192

The synthesis of 9-(1,4-dihydroxybut-2-oxypurines commenced with 2-butene-1,4-diol (**1004**) and via **1005** to **1006**, which upon reaction with **1007** gave **1011** and then, upon hydrolysis, the racemic alkoxyamine **1012**. The chiral derivatives commenced with the enantiomers of malic acid (**1009**) through **1010** to **1008**, as shown in the scheme. Treatment of **1012** with **996** and further transformations followed almost the same sequence as before to give **1013**.

An alternative strategy for the synthesis of 9-alkoxypurines is via the coupling of a suitably functionalized 9-hydroxypurine with protected alcohols such as **1014** under the Mitsunobu condition or with halides under base-catalyzed conditions to give after deprotection **998** or its adenosine analog **1015** (90TL2185).

The 5-iodo derivative **1016** was prepared by reaction of the acetate of **999** with iodine monochloride, and subsequent deprotection using sodium methoxide in methanol. The protected derivative **1016** is a suitable precursor for use in cross-coupling reactions to prepare the unsaturated analogs **1018** and **1019**. Thus, reaction of **1016** with methyl acrylate in the presence of palladium(II) acetate gave the (*E*)-5-(2-methoxycarbonylvinyl)uracil **1017**; this was converted into the (*E*)-5-(2-bromovinyl) analog **1019** by alkaline

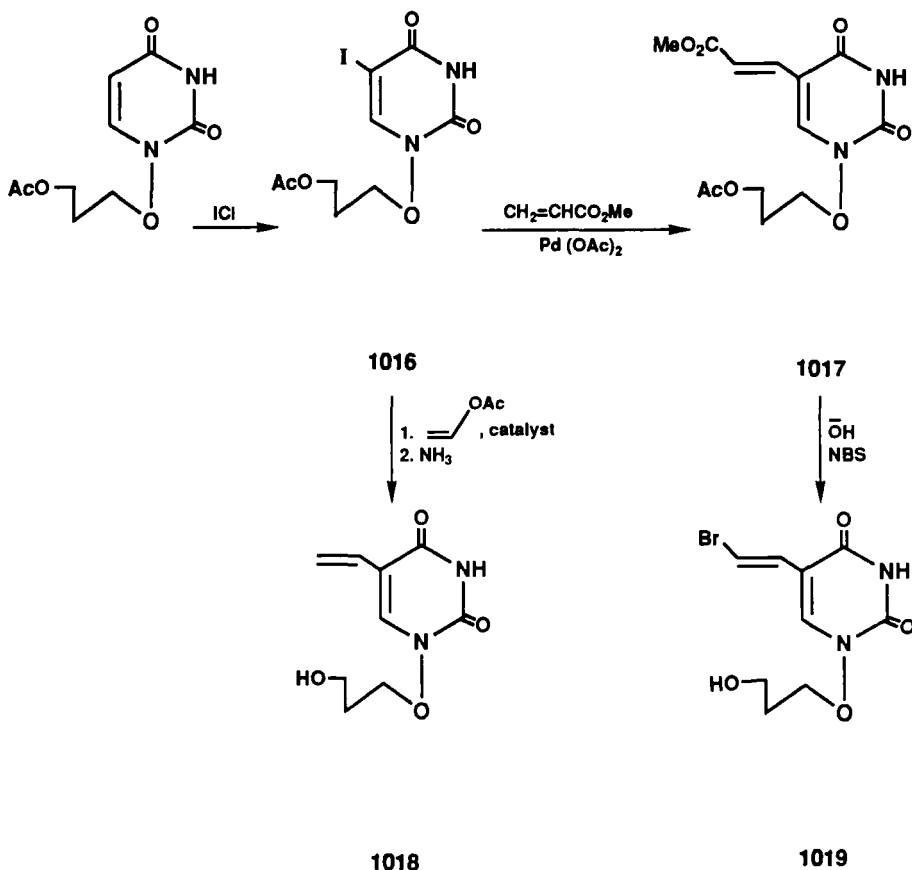


SCHEME 193

hydrolysis followed by treatment with *N*-bromosuccinimide. In a related reaction sequence, the 5-vinyl derivative **1018** was prepared by reaction of **1016** with vinyl acetate in the presence of preactivated diacetato-bis(triphenylphosphine)palladium(II) catalyst. Deprotection with ammonia gave the required acyclopyrimidine [90JCS(P1)2175].

Replacement of the oxygen with a nitrogen in the last group of translocated analogs could be achieved by reacting the *N*-amino heterocycle with the respective aldehyde adopting the same strategy used earlier (88TL5995).

The 9-alkoxyguanine **998** has potent and selective antiherpes virus activity. The racemic guanine derivative **1003** showed potent and selective activity against herpes simplex virus type 1 and 2, but was less active against varicella zoster virus (VZV). Its antiviral activity is attributable to the *S*



SCHEME 194



isomer, which was found to be more active than acyclovir against HSV-1 and HSV-2 and about four times less active than acyclovir against VZV. The *S* enantiomer of guanine **1013** is only weakly active against HSV-1 and inactive against HSV-2; it is about twice as active as acyclovir against VZV (91JMC57, 91MI2).

### B. 2',3'-, 3',4'-, AND 4',5'-TRISECO-NUCLEOSIDES (TYPE 3.2)

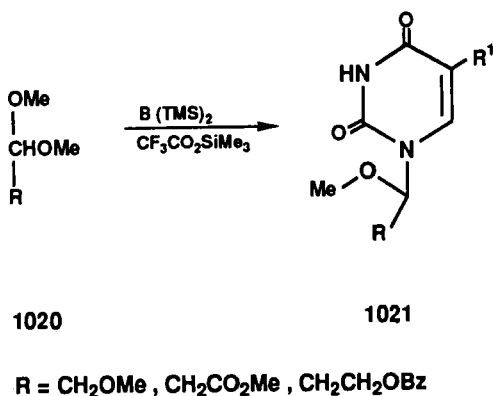
The acetals **1020** reacted with a silylated base to give **1021** (91CB2019, 91CB2641). The same type of reaction was also used to prepare other types of acyclic nucleosides.

### C. 3',4'-, 4',5'-, AND 4',X-TRISECO-NUCLEOSIDES (TYPE 3.3)

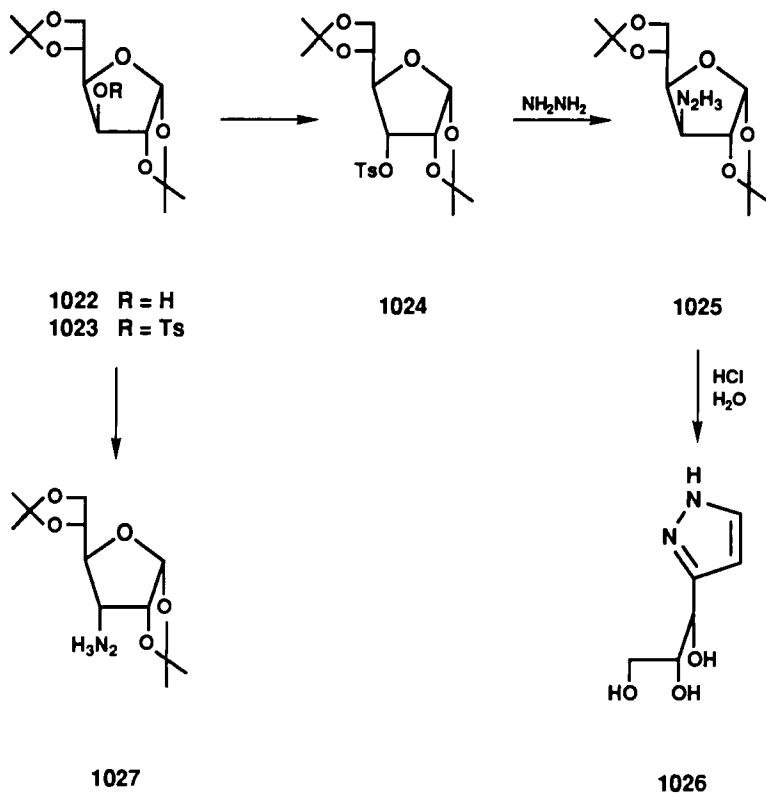
This group of nucleosides could also be named glycerolyl heterocycles. A modified procedure for the synthesis of the pyrazole nucleoside **1026** was carried out by the hydrazinolysis of the epimeric hydrazine **1025**, obtained from **1024**, by hydrolysis with HCl. The use of **1025** is more efficient than using **1027** obtained from the hydrazinolysis of **1023**, which in turn was obtained from **1022** [75JHC75; 85JCS(P1)1425].

Regioselective cyclocondensation of 3-ketoglucose with hydrazines gave the corresponding *C*-nucleosides **1028** and **1029** (92RTC427).

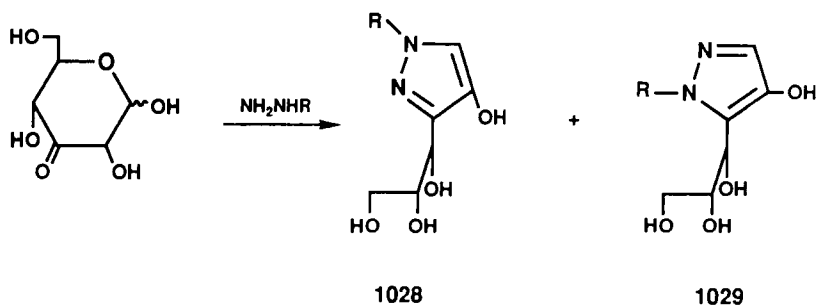
Reaction of 1-alkylamino-1-deoxy pentuloses **1030** with KCNS gave **1031** (84AQ102).



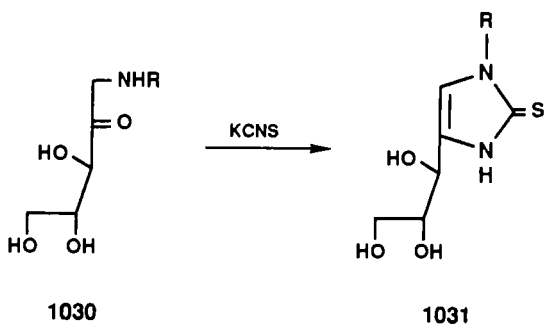
SCHEME 195



SCHEME 196

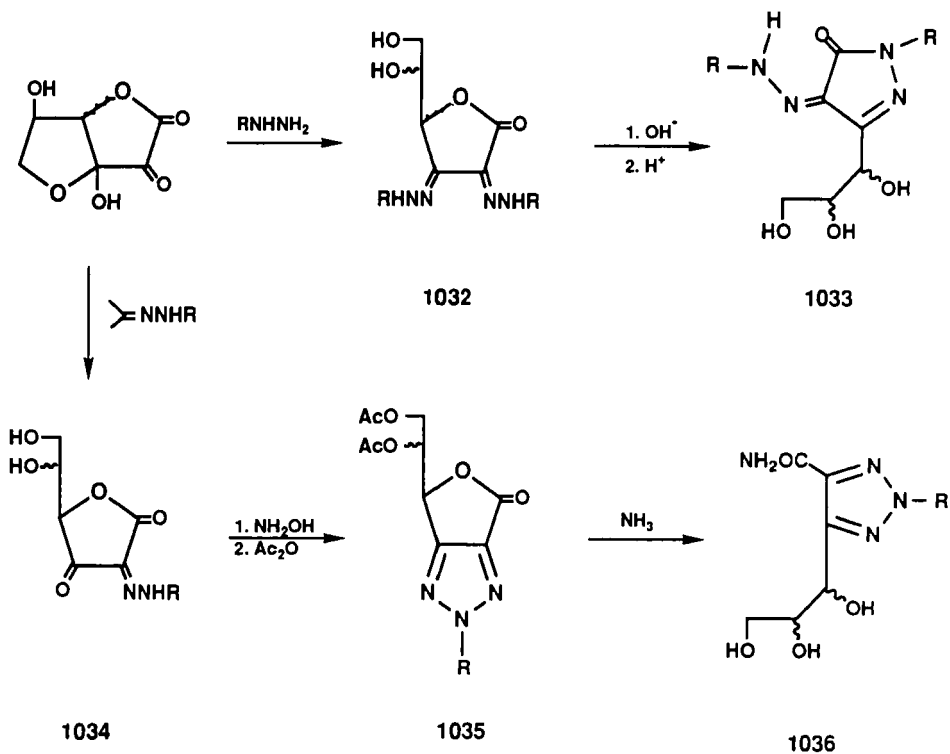


SCHEME 197



SCHEME 198

L-Ascorbic acid and its analogs are excellent precursors for this type of acyclonucleoside. Thus, reaction of their oxidation products with arylhydrazines gave the bis-hydrazones **1032**, whose rearrangement with alkali

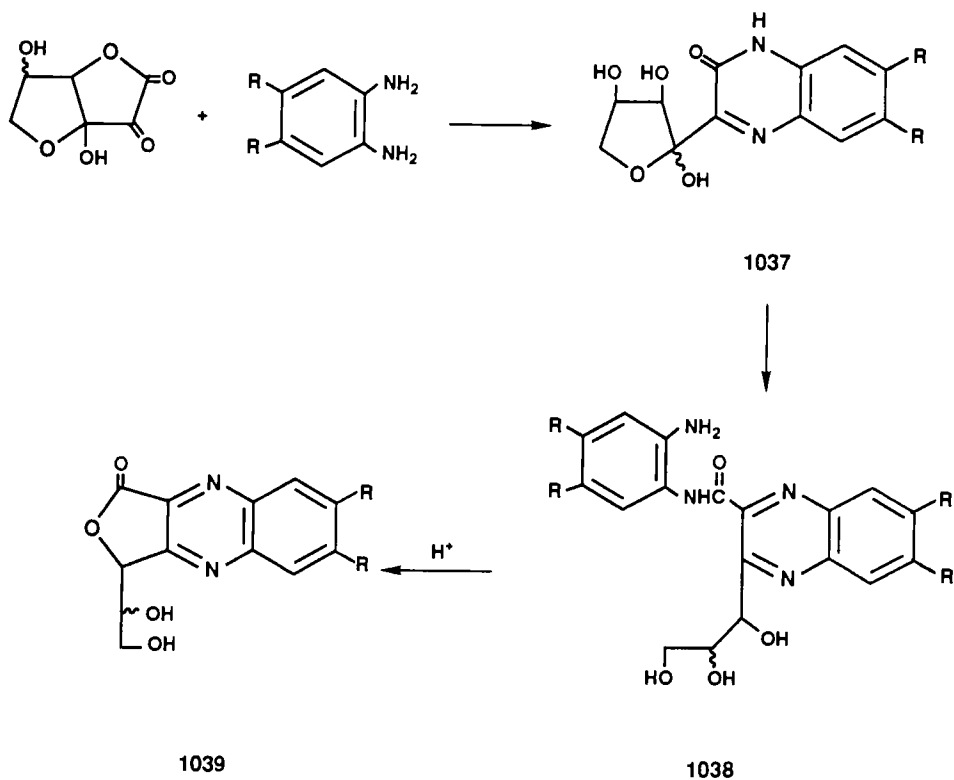


SCHEME 199

and acidification gave the pyrazolines **1033**. The various possible isomers were prepared from the respective ascorbic analogs [68JCS2248; 72MI1; 76CI(L)372, 76MI1, 76MI2; 77MI1, 77MI3; 78MI1, 78MI3; 80MI1; 86MI6; 88G687, 88MI6]. The acetals of **1033** were prepared [86MI2; 87MI3; 88JCS(P1)133, 88JCS(P1)139, 88MI3; 94MI2; 95MI1]. Reaction of **1033** with HBr/AcOH provide 1,3-dibromodideoxyglycerolyl derivatives suitable for further modifications (80MI2; 92MI3, 92MI5).

When dehydroascorbic acids were reacted with acetone arylhydrazones, they gave the respective monohydrazones **1034** (92AHC233), whose reaction with hydroxylamine gave the corresponding C-3 oxime, which readily underwent dehydrative cyclization with a simultaneous acetylation when treated with acetic anhydride to give **1035**. Ring opening of the lactone and deacetylation with ammonia afforded triazole **1036** (77MI2).

Reaction of dehydro-L-ascorbic acid and its analogs with two molecules of *o*-phenylenediamine or its substituted derivative gave the quinoxaline

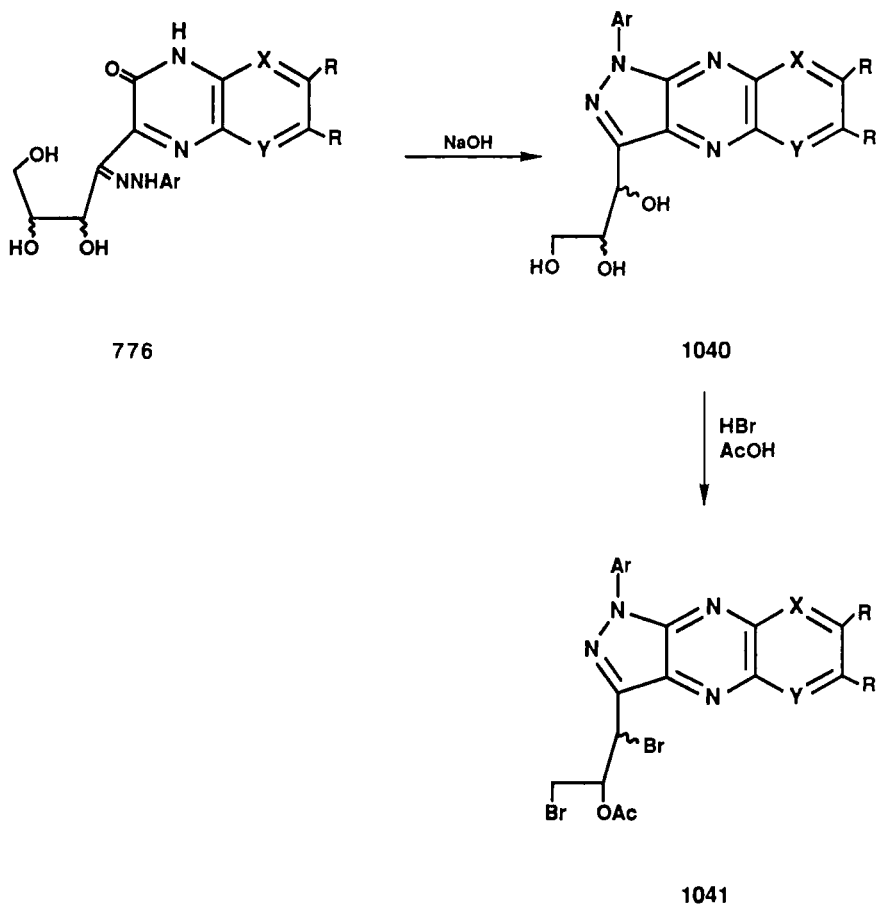


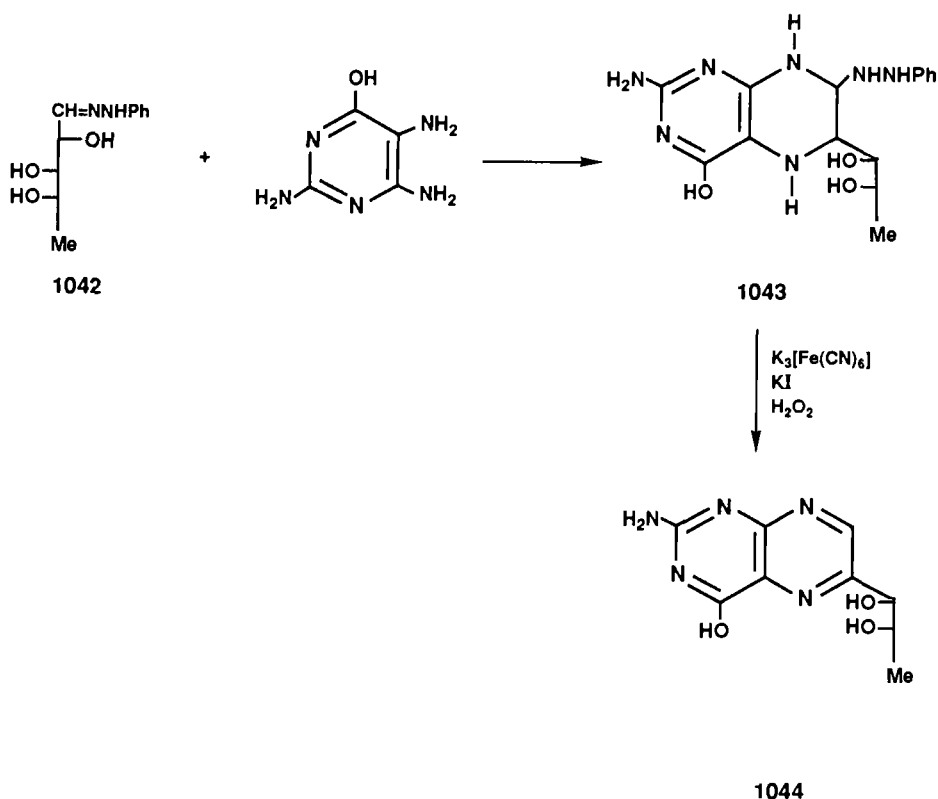
SCHEME 200

derivative **1038** via **1037**, whose treatment with acid led to a splitting of the amide diamine residue, giving a lactone **1039** (86MI5; 92AHC233, 92MI6).

Dehydrative cyclization of **776** with alkali afforded the pyrazoloquinoxalines **1040** with various configurations of the hydroxyl groups (78MI2; 86MI7, 86G721; 89MI1–89MI4; 90MI3). The reaction of **1040** with HBr/AcOH gave 1,3-dibromodideoxyglycerol analogs **1041**. The respective aza analogs were similarly prepared (X or Y = N) (96UP2).

The condensation of 2,4,5-triamino-6-hydroxypyrimidine and 5-deoxy-L-arabinose phenylhydrazone **1042**, followed by oxidation of the intermediate **1043**, gave biopterin **1044**. The tetrahydrobiopterin is the natural cofactor of phenylalanine hydrolase. Various stereochemical isomers were also pre-





SCHEME 202

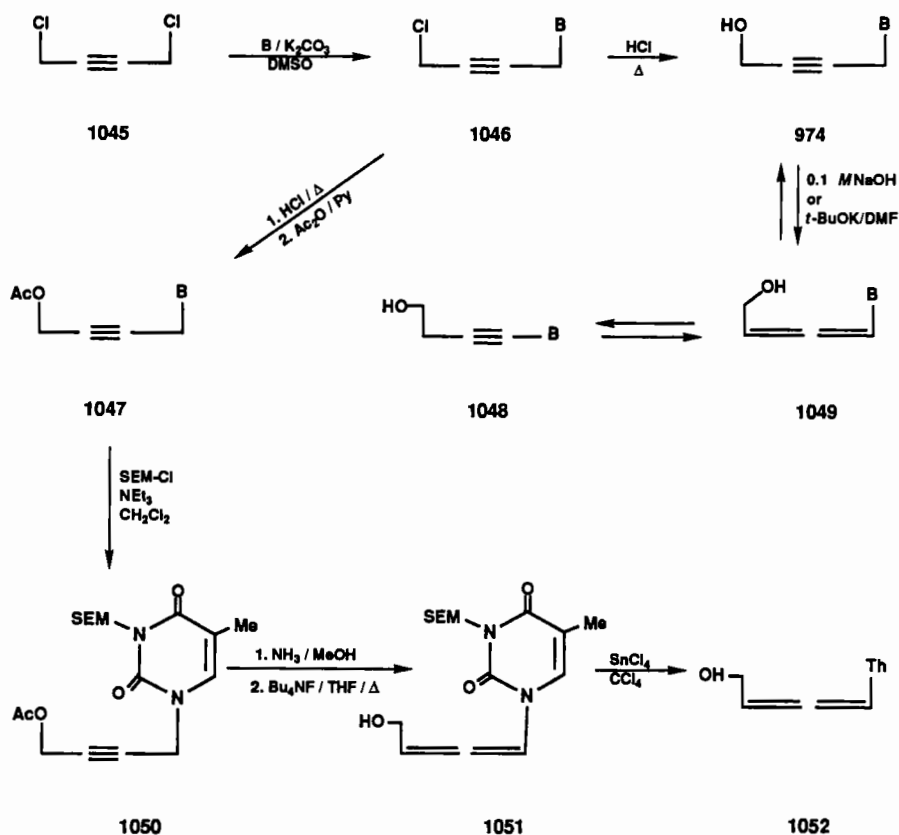
pared (79BCJ181). Bicyclomycin derivatives could also be considered as acyclonucleosides (83TL5607).

The EHNA analogs are considered as *diseco* nucleosides, however the 9-(2-hydroxy-3-butyl)adenine can be categorized as *triseco* nucleoside (74JMC6).

#### D. 1',x-, 4',x-, AND 4',5'-TRISECO-NUCLEOSIDES (TYPE 3.4)

This group of nucleosides is known as allenols because they are derived from nucleic acid bases such as adenallene, cytallene, and guanallene. They were prepared by alkylation of bases or a suitable precursor with 1,4-dichloro-2-butyne (**1045**) to give **1046**. Hydrolysis with acid gave **974**, accompanied in the case of 2-amino-6-chloropurine by restoration of the guanine moiety. Acetylene-allene isomerization led to mixtures containing the al-

lenols **1049** as major products in addition to **974** and **1048**. The reaction must be conducted under strictly controlled conditions [87MI1; 89JA5925; 91MI6]. The synthesis of thymallene could not be accomplished as described earlier. Thus, protection of acetate **1047** with a  $\beta$ -(trimethylsilyl)ethoxymethyl group afforded **1050**, whose deacetylation and isomerization with  $\text{Bu}_4\text{NF}/\text{THF}$  gave **1051** and then, upon deprotection, **1052** (89JOC3675). The allenols are resolvable into *R*- and *S*-enantiomers. Chromatography and adenosine deaminase could be used in this respect (92JMC4098). The racemic form exhibits strong anti-HIV activity (88PNA6127; 89MI6). The *R*-Adenallene displayed a significantly greater effect against HIV-1 infection of TH8 cells than the *S*-enantiomer. They inhibit replication and the cytopathic effect of human immunodeficiency virus *in vitro* (88PNA6127).



SCHEME 203

## V. *tetraseco*-Nucleosides from Four Bond Disconnections

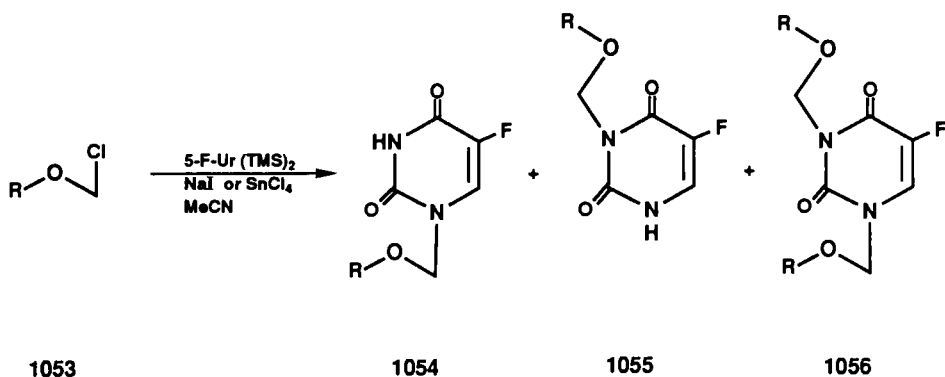
### A. 1',2'-, 2',3'-, 3',4'-, AND 4',5'-*TETraseco*-NUCLEOSIDES (TYPE 4.1)

This type of nucleoside includes numerous simple derivatives of heterocyclic compounds. Only a few examples are given. Condensation of the chloromethyl ethers **1053** with silylated 5-fluorouracil gave the two mono- and one disubstituted derivatives **1054**, **1055**, and **1056**, respectively (86MI3).

### B. 2',3'-, 3',4'-, 4',x'-, AND 4',5'-*TETraseco*-NUCLEOSIDES (TYPE 4.2)

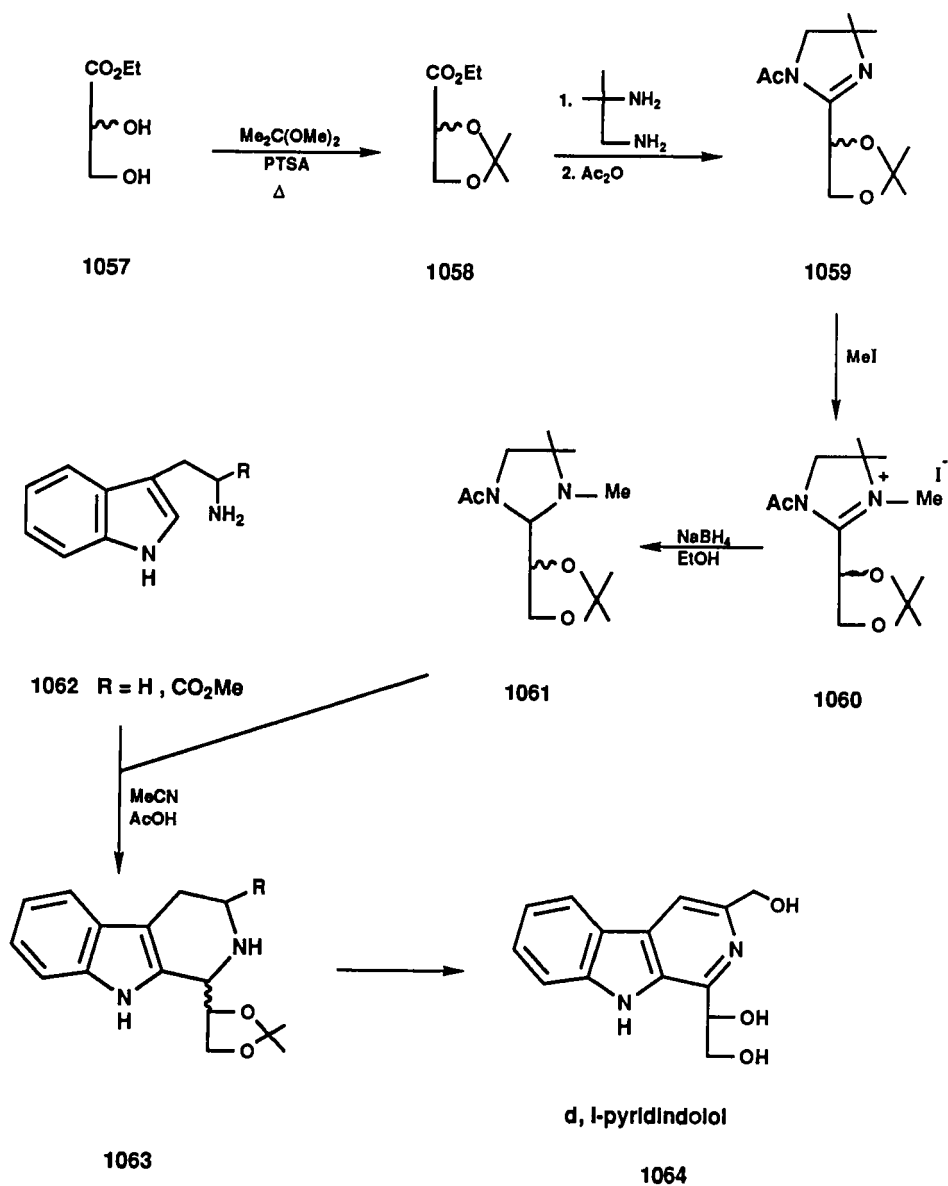
The synthesis of *d,l*-pyridindolol **1064** started by acetonation of glyceric ester **1057** to give **1058**, which was converted to the imidazoline **1059** by reaction with 1,1-dimethyl-1,2-diaminoethane followed by acetylation. Its methylation gave **1060**, which can be reduced to **1061**; further reaction with tryptamine or tryptophan ester hydrochloride **1062** gave the respective diastreomeric mixture of carboline **1063** (80H947). Its conversion to racemic alkaloid *d,l*-pyridindolol **1064** could be readily achieved (79JOC535).

Reaction of the olefin **1065**, obtained from tosylate **1023**, with hydrazine gave the pyridazine **1066**, whose deisopropylidenation gave **1067** (75JHC75).



SCHEME 204

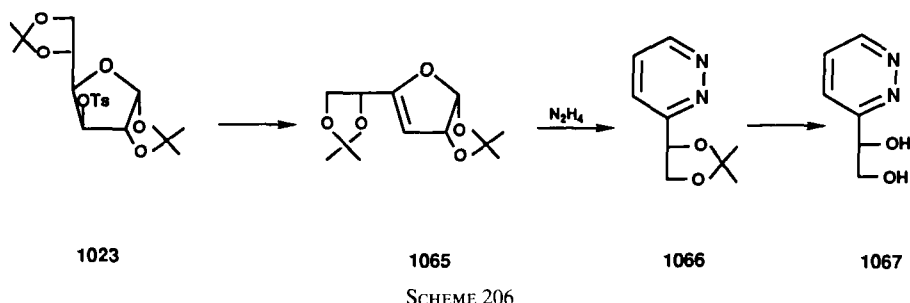




SCHEME 205

## C. 1',x-, 3',4'-, 4',x-, AND 4',5'-TETRASECO-NUCLEOSIDES (TYPE 4.3)

This group represents the most important group of the four-bond-disconnections class.



### 1. Acyclo-*N*-nucleoside Analogs

This type of acyclonucleoside was prepared by the reaction of racemic tosylate **1068** with base on the presence of  $\text{Bu}_4\text{N}^+ \text{HSO}_4^-$  or  $\text{NaH}$  to give **1069**, which was deblocked by  $\text{HCl}$  or  $\text{AcOH}$  to give **1070** (82LA1940, 82AAC55; 83JHC295; 85JMC467; 96UP1). The synthesis of (*S*)-9-(2,3-dihydroxypropyl)adenine (*S*-DHPA) started with 1-*O*-*p*-toluenesulfonyl-2,3-*O*-isopropylidene- $\beta$ -glycerol (75CCC187). The racemic form as well as the *S*-DHPA inhibited vaccinia, HSV-1, HSV-2, vesicular stomatitis, and measles, whereas the *R*-isomer was inactive (79JMC510).

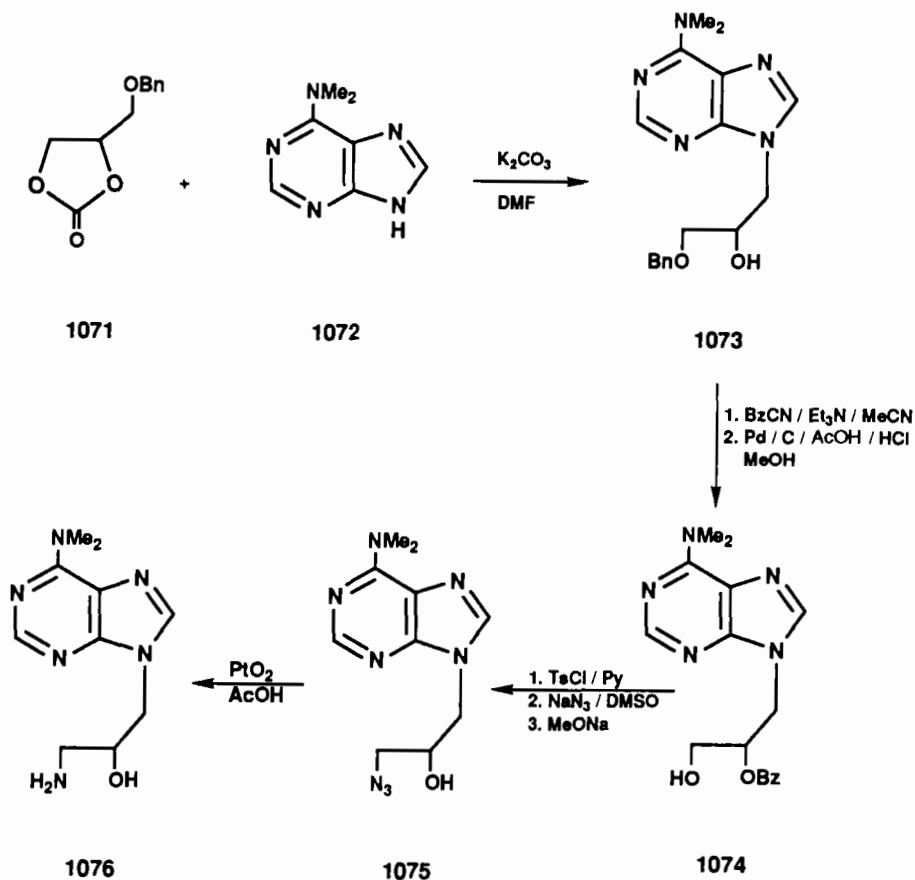
The aminopuromycin analog **1076** was prepared in a similar manner to that developed for 9-(3-amino-2-hydroxypropyl)adenine (78CCC3444). The starting 4-benzyloxymethyl-2-oxo-1,3-dioxalane (**1071**) was condensed with **1072** to give **1073**, which was benzoylated and then debenzoylated to give **1074**. Conversion to the azide **1075** followed by reduction gave **1076** (83JHC295).

The acyclic benzimidazole or benztriazole nucleosides were prepared by condensation of their trimethylsilyl derivatives with the alkylating agents **1077** or by direct alkylation of their sodium salts (88KGS198; 88KGS632) to give **1078**, whose deacetylation gave **1079**. The benzimidazole derivatives did not exhibit *in vitro* activity against herpes simplex virus type 1 or influenza virus (84MI1). The antileishmanial and antitrypanosomal activity of the pyrazolopyrimidine derivatives were evaluated (90MI5).

The synthesis of *R*-DHPA started with **1080**, whose coupling with adenine gave **1081**. The latter, upon deisopropylidenation, periodate oxidation, and reduction, gave **1082**, which was hydrolyzed to *R*-DHPA (**1083**) (75CCC187).

Several 9-(2',3'-*O*-isopropylideneglycerolyl)-8-azahypoxanthine and 8-aza-adenines were synthesized by a 1,3-dipolar cycloaddition of racemic or (*S*)-1-azidoglycerolyl derivative **1084** with the sodium salt of malononitrile or cyanoacetamide to afford the intermediate triazoles **1085** and **1088**, which



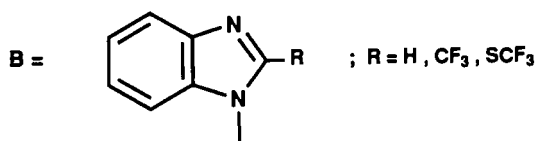
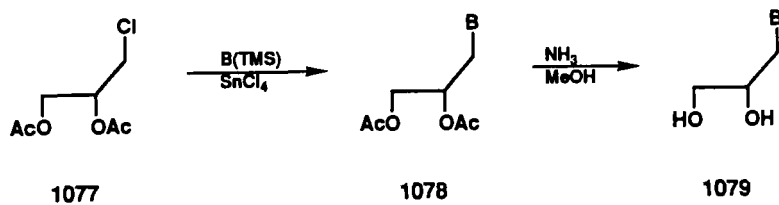


SCHEME 208

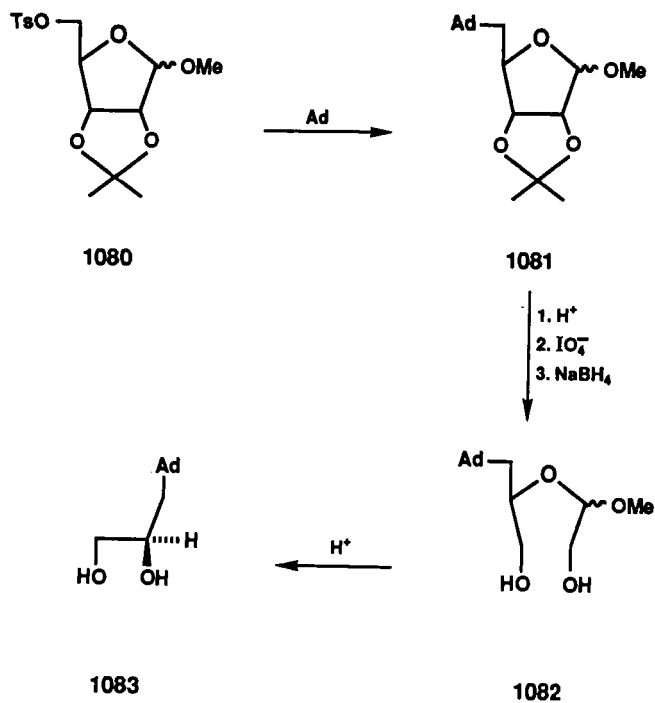
esterification did not give **1092**. The racemic **1095** was inactive in tissue culture against herpes virus type-2, rotavirus, poliovirus, and parainfluenza virus.

Alkylation of the uracil derivatives with the epoxide **1097** gave **1098**, whose hydroxylation gave **1099**, which had no significant activity against herpes simplex virus type 1 (94MI6). Uracil derivatives derived from **1068** were also prepared.

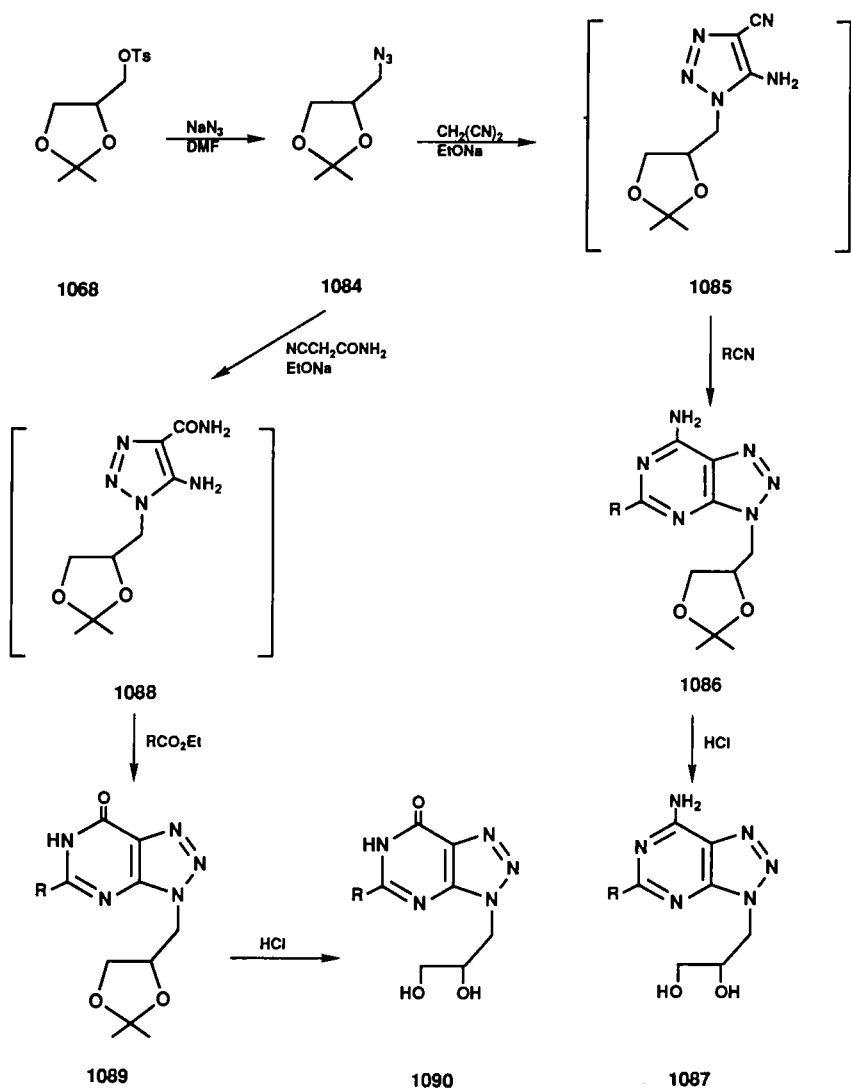
The first synthesis of racemic DHPA was done by constructing the heterocyclic ring onto amine **1100** (65JMC502). This was done by a reaction with 5-amino-4,6-dichloropyrimidines, followed by construction of the imidazole



SCHEME 209

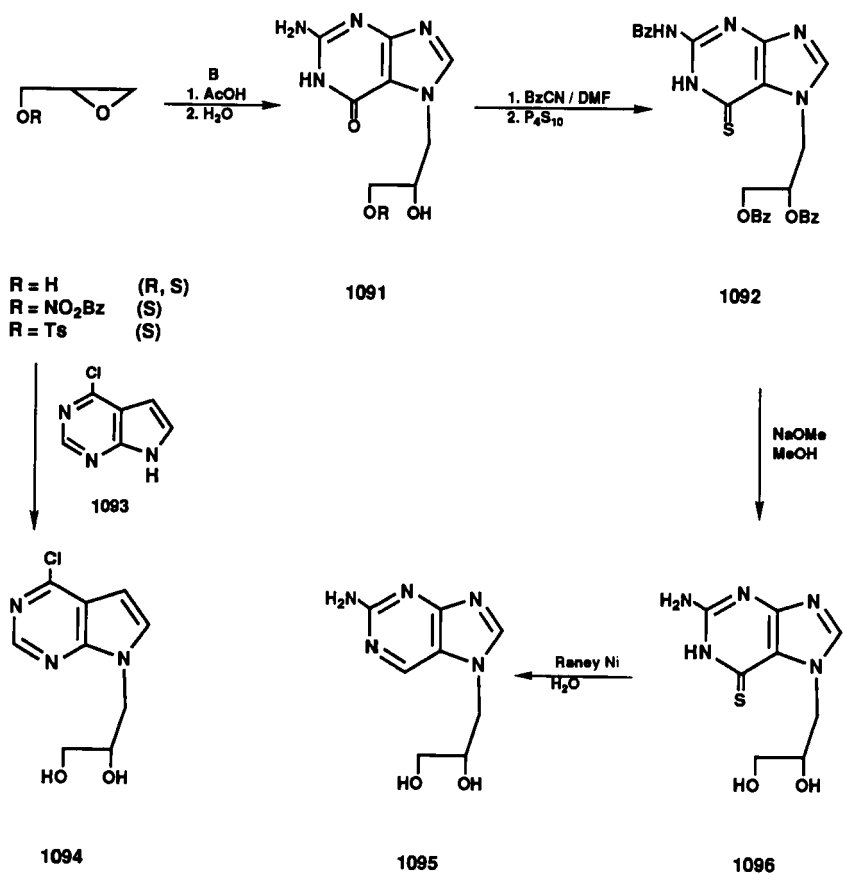


SCHEME 210

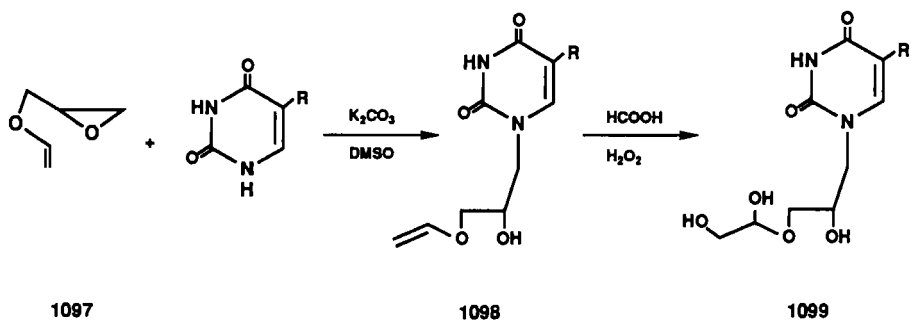


SCHEME 211

ring with triethyl orthoformate to give **1104**, which upon aminolysis and hydrolysis gave **1105**. Alternatively, it was prepared from 4-chloro-6-ethoxy-5-nitropyrimidine by a reaction with **1100** to give **1103**, which cyclized to **1106** and then was aminolized to **1105**. Reaction of 2-amino-



SCHEME 212



SCHEME 213

4,6-dichloropyrimidine with 3-amino-1,2-propanediol (**1100**), followed by a reaction with a diazonium salt and then reduction, gave **1101**, which cyclized to **1102**. Hydrolysis of **1102** gave **1107** ( $Y = O$ ), and its treatment with thiourea gave **1107** ( $Y = S$ ) (90JHC1409).

The 3'-fluorodeoxy analog **1109** was prepared by the reaction of base with the oxirane **1108**, whereas the 2'-fluorodeoxy analog **1113** was prepared by opening the oxirane ring to give **1110** followed by tosylation to give **1111**. The latter reacted with the sodium salt of the base to give **1112**, which upon hydrogenolysis gave **1113** (92CCC1466). A great number of bases were treated in this manner.

Bromination of **1114** gave 1-(3-bromo-2-oxopropyl)pyridazin-6-ones (**1116**) as a major product in addition to **1115** (91JHC385). Reaction of **1116** with sodium azide gave the corresponding 1-(3-azido-2-oxopropyl)pyridazin-6-ones **1117**, which was reduced to **1118**. 4,5-Dichloro-1-(2,3-dihydroxypropyl)pyridazin-6-one **1121** was also prepared from **1116** via **1119** and the corresponding 2,3-epoxypropyl derivative **1120** (91JHC1235).

The condensation of various heterocycles (pyrimidine or purine) with allyl bromide has been effected in the presence of KI. This selectively afforded N-1 isomers with pyrimidines, but N-9, N-3 or N-9, N-7 isomer mixtures with purines (88MIP1; 89MI12; 91MI1). Alkyl esters of 3-adenin-9-yl-2-hydroxypropanoic acids were reported as broad-spectrum antiviral agents (85JMC282).

## 2. *Acyclo-C-nucleoside Analogs*

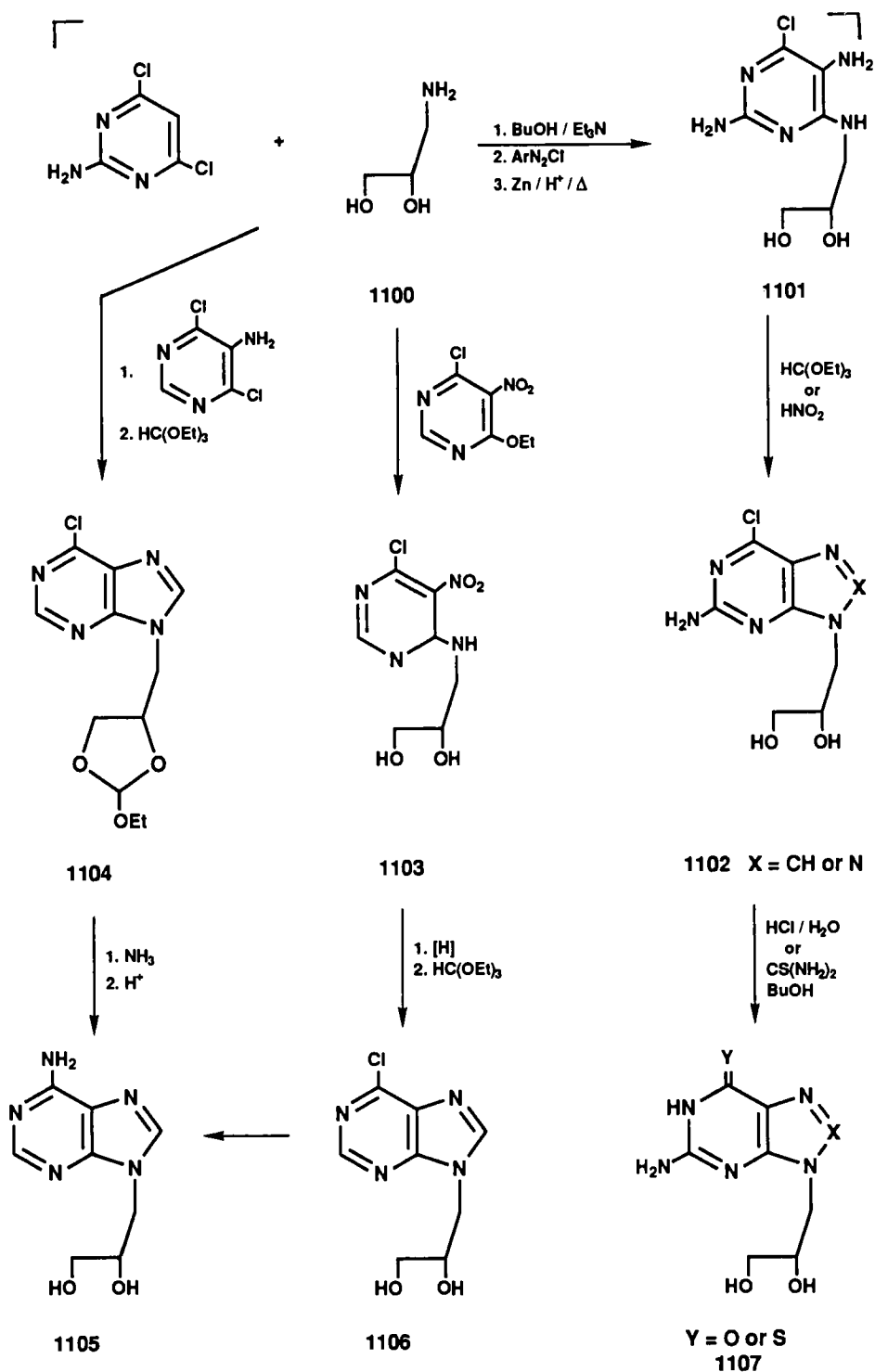
C-Acyclic nucleoside analogs of inosine and guanosine 8-[(*RS*)-2,3-dihydroxypropyl]imidazo[1,5-*a*]-1,3,5-triazin-4(3*H*)-ones were synthesized. The route involved the cyclization and rearrangement of 5-acylamino-5-allyl-6-amino-4,5-dihydropyrimidin-4-ones (**1122**) to 8-allylimidazo[1,5-*a*]-1,3,5-triazin-4(3*H*)-ones (**1123**). Osmium tetroxide hydroxylation gave **1124**. None of these analogs showed appreciable antiviral or antitumor cell activity (84NAR263; 87MI6).

The acyclic nucleosides **1126** and **1127** were prepared from the glyceraldehyde derivative **1125** through the steps shown in Scheme 218 (88JOC2413). Scheme 219 shows the synthesis of **1128** and **1129** [91JCS(P1)195].

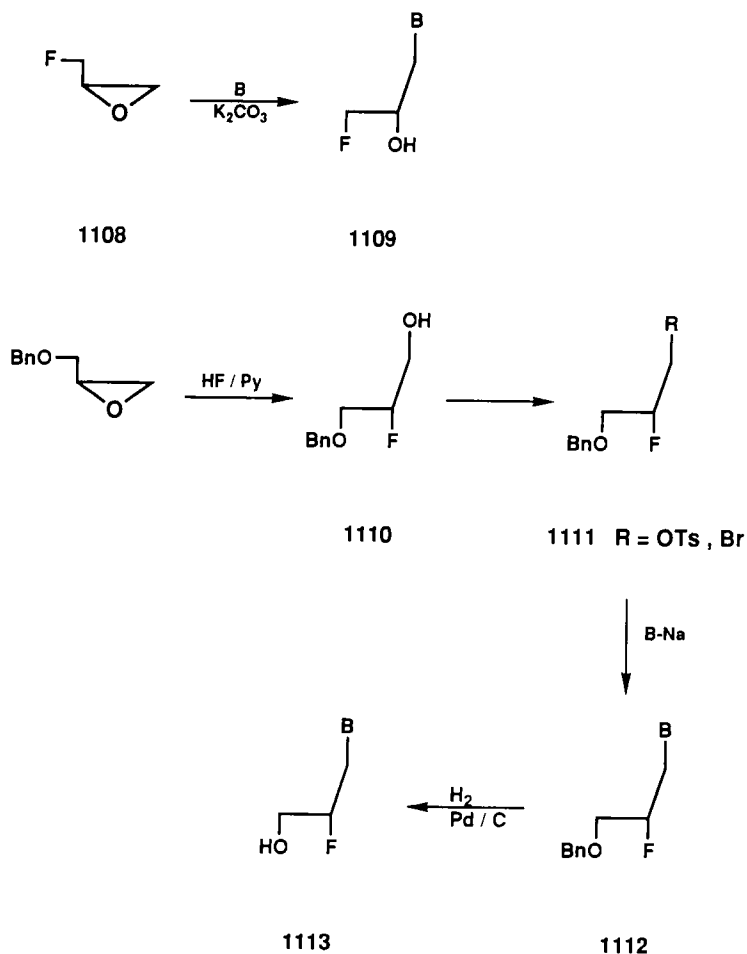
Pyrazole **1131** was prepared from the mesylate **1130**, which proved to be an excellent precursor for this type of nucleoside as in **1132**. The construction of the pyrimidine ring was achieved through the steps shown in Scheme 220 to give **1133** and **1134** [85JCS(P1)1425; 89JCS(P1)925].

Reaction of the 3-deoxypentosulose **1135** with aminoguanidine under physiological conditions gave a mixture of the two triazines **1136** and **1137** (91MI10).





SCHEME 214

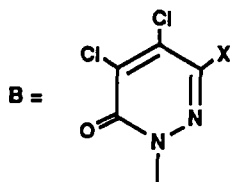
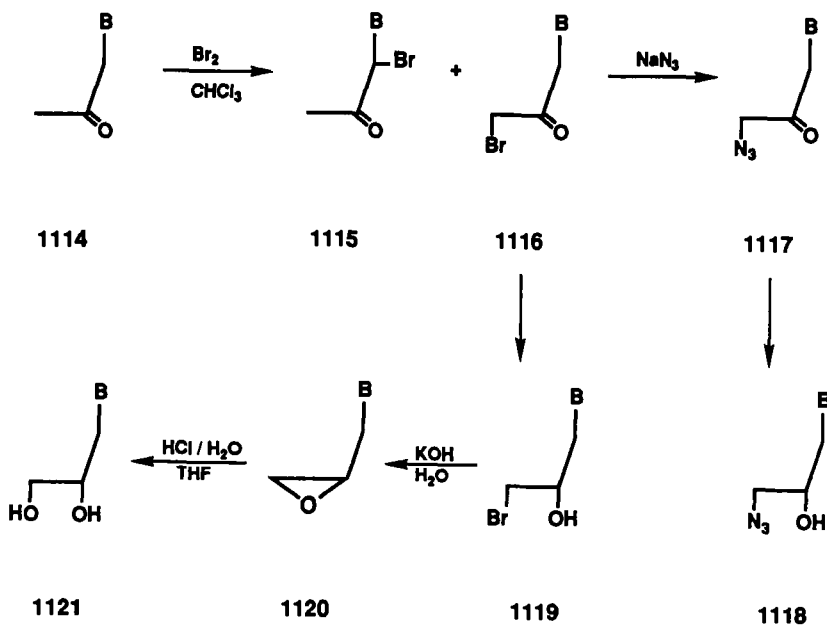


SCHEME 215

## VI. *pentaseco*-Nucleosides from Five Bond Disconnections

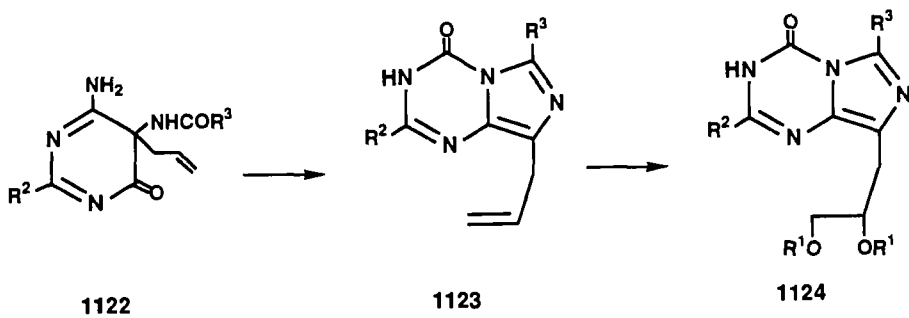
### A. HYDROXYMETHYL DERIVATIVES

It is doubtful whether these should be considered as nucleosides. However, they are readily prepared from *C* polyhydroxyalkyl derivatives (type 1.5) by periodate oxidation and reduction. They are also prepared by hydroxymethylation of the respective heterocycles (86MI4).



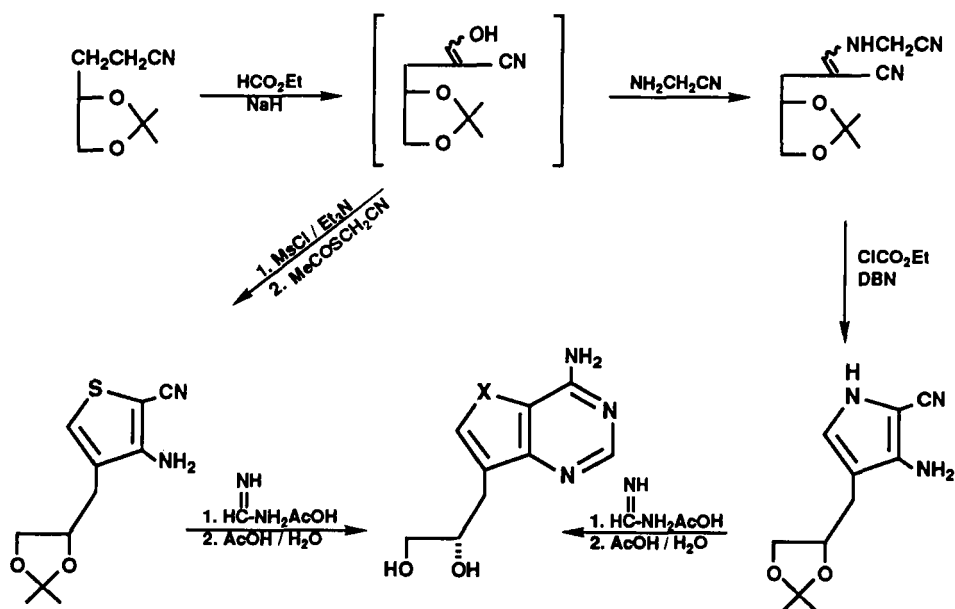
X = H, NO<sub>2</sub>

SCHEME 216



SCHEME 217





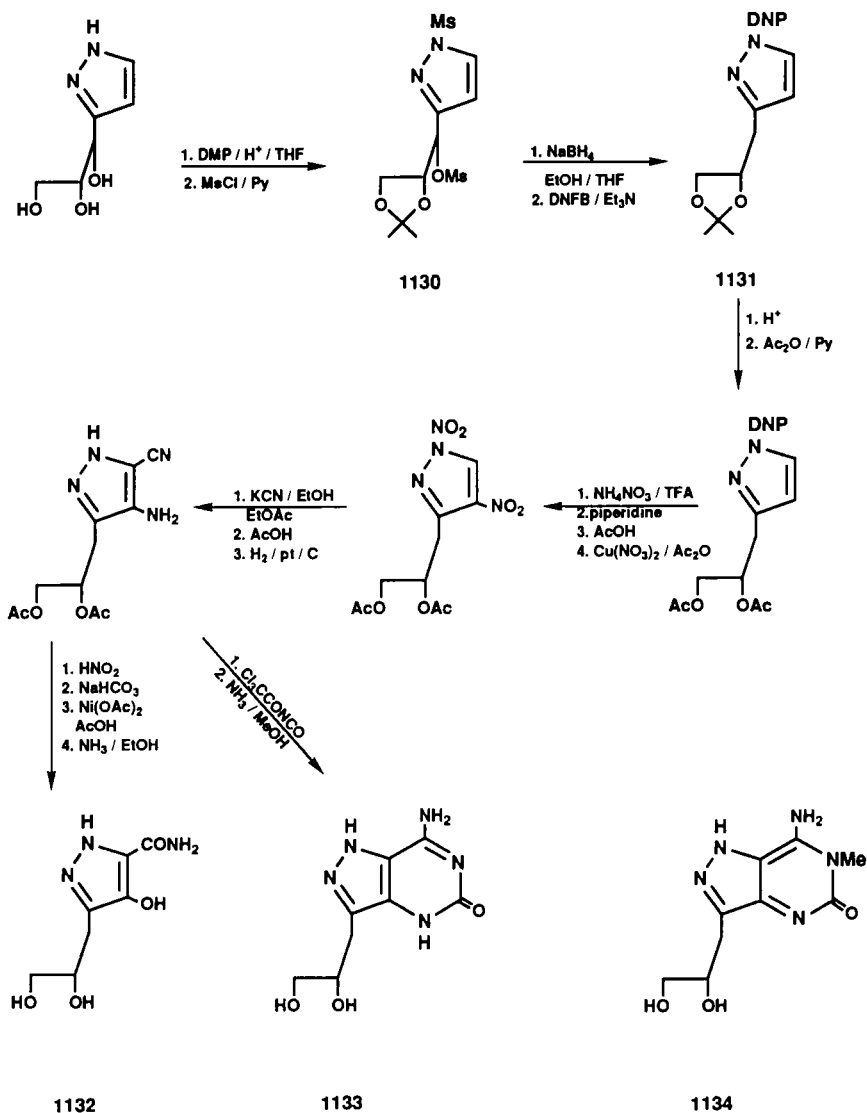
SCHEME 219

## B. HYDROXYETHYL DERIVATIVES

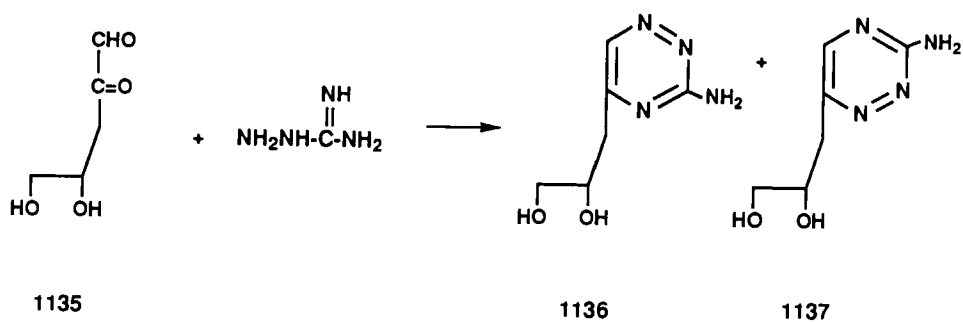
The 7-(2-hydroxyethyl)guanine derivative **1139** was obtained in two steps from guanosine (**1138**) (61JCS3923). Benzoylation of **1139** followed by thiation gave **1140**, which upon debenzoylation gave **1141**, whose dethiation was affected to give **1142** (89MI8).

Alkylation of the base by the tosyloxy derivative **1143** gave **1144**, whose hydroxylation gave **1145**, which had no significant activity against herpes simplex virus type 1 (84FES346).

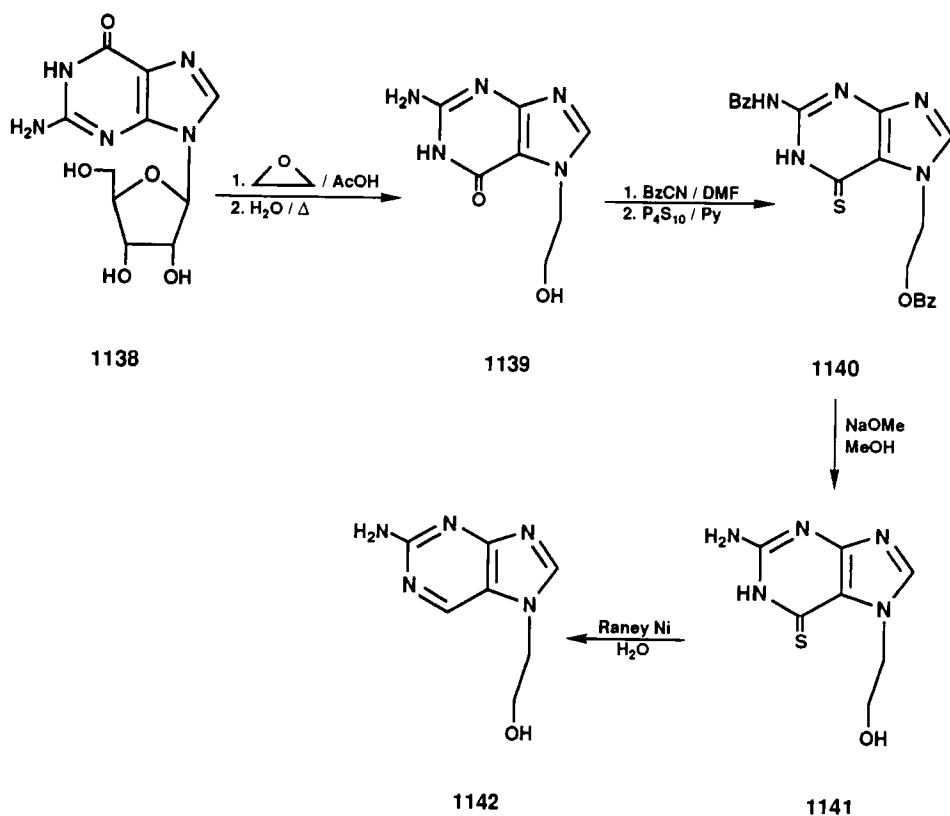
Tosylation of **1146** gave **1147**, which was converted to the iodo derivative, whose reaction with the sodium salt of guanine, followed by acetylation to aid its purification and then deprotection, gave **1148** (86JMC1384). The hydroxymethyl groups on C-5 of barbituric acid were introduced starting with malonic ester and then reaction with urea (93MI12).



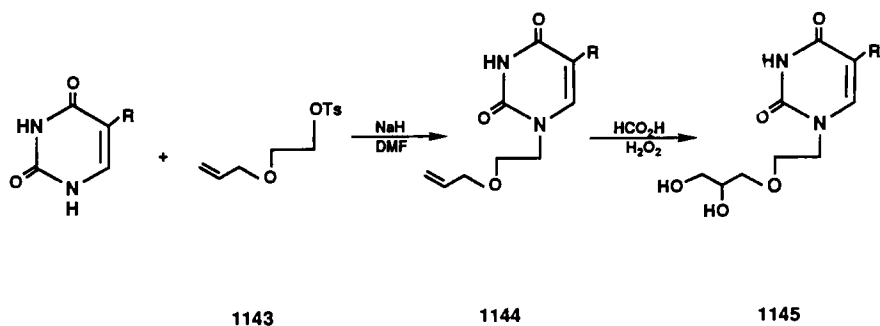
Alcohol **1149** unexpectedly gave mesylate **1150** upon treatment with MsCl. The mesylate group could be displaced with methanethiolate to give **1151**, also prepared from alcohol **1152** via **1153** [93JCS(P1)1109].



SCHEME 221



SCHEME 222



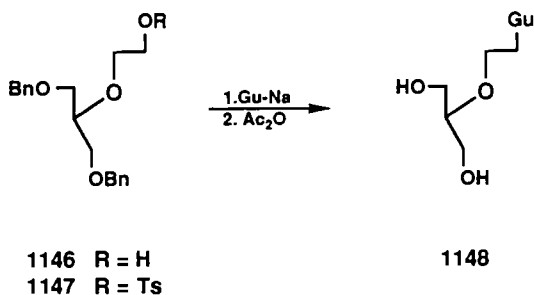
SCHEME 223

## VII. Appendix

The literature cited in *Chemical Abstracts* (Vol. 119–122) is included under this appendix. A review of the structure, antiviral, activity, and, to a certain extent, the chemistry of acyclic nucleosides has appeared (93MI5). A number of publications reported on the antiviral activities and biological evaluations of acyclic nucleosides (93AAC2247; 93MI1; 93MI2; 93MI7, 93MI10; 94MI5; 94MI16). Structure–activity relationships for some antiviral acyclic nucleosides using electric field mapping were studied (93MI9).

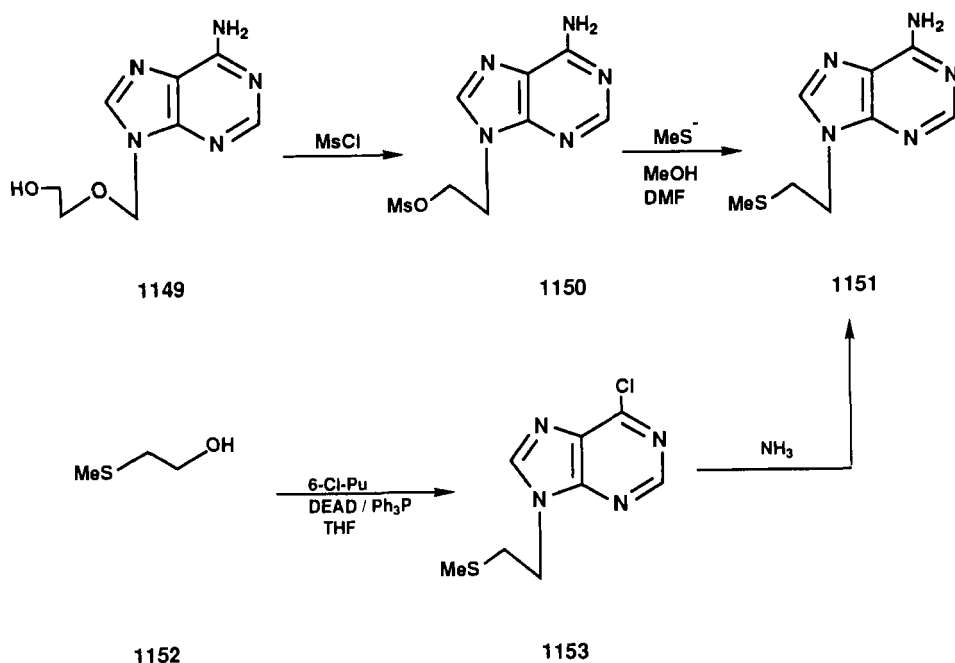
Optically active *seco*-nucleosides of type 1.1 of 2-nitroimidazole were prepared from tartaric acid ester by conversion to the dioxolan followed by reduction and acylation to give **1154**, which was converted to **1155**. Its coupling and deacylation gave **1156** (94MIP1). All the optically active isomers showed a radiation-sensitization effect equivalent to that of the racemate.

5,6-Dichlorobenzimidazole nucleosides of type 1.2 were prepared (94MI4). The thymine analog, upon selective protection, oxidation, and



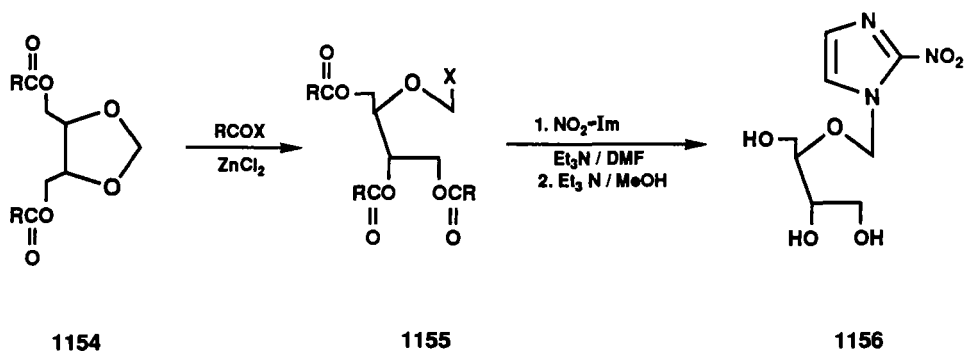
SCHEME 224



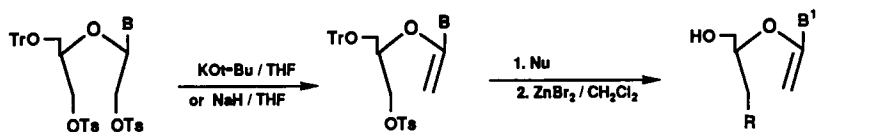


SCHEME 225

then reaction with a Wittig reagent, afforded derivatives of acyclic analogs (94T5279). The 1',2'-unsaturated *seco*-adenosine and *seco*-uridine analogs **1159** were synthesized by the base-promoted regioselective elimination of the corresponding 2',3'-ditosylates **1157** (94TL3987). Nucleophilic substitution of the tosyl group in **1158** by azide or halide ions or heating the tosylate in aqueous DMF gave the respective nucleoside analog.

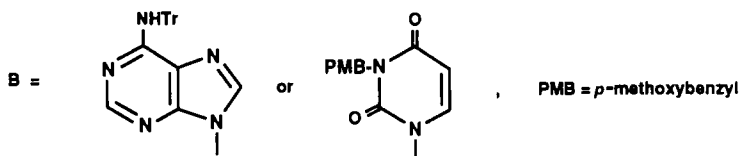


SCHEME 226



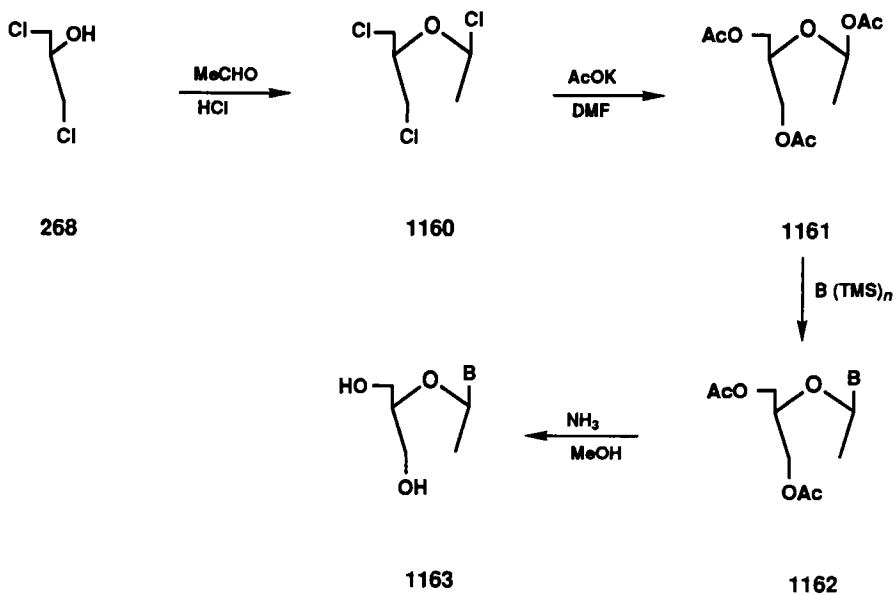
1157

1158

1159 R = Cl, N<sub>3</sub> or OH

SCHEME 227

A series of the nucleic acid bases of the racemic 2'-deoxy-2',3'-*seco*-nucleosides were prepared starting with 1,3-dichloro-2-propanol, which was converted to **1160** and then to **1161**. The condensation of the silylated bases



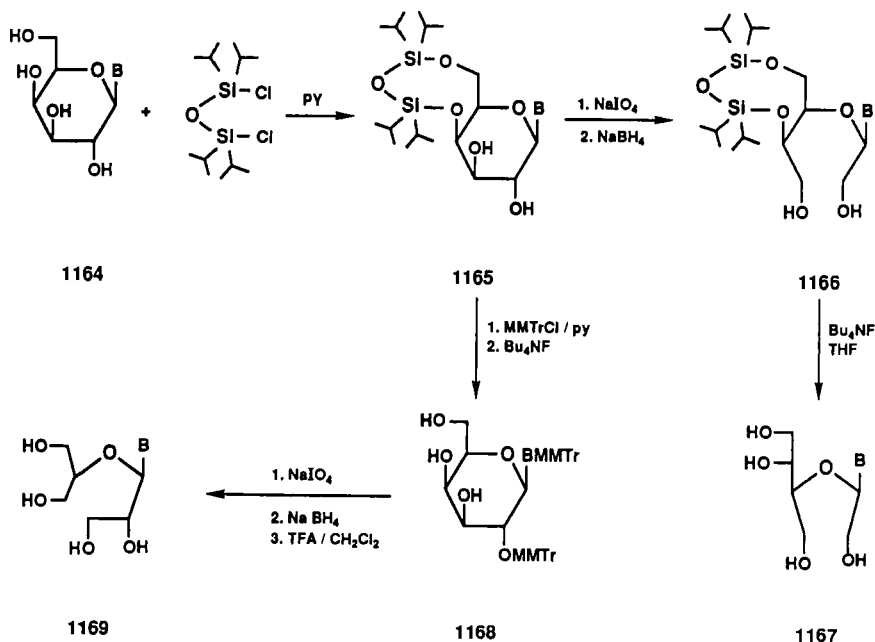
SCHEME 228

was carried out with **1161**, except for the cytosine analog, whose sodium salt was condensed with the trichloro derivative **1160** (93MI8). Deprotection gave **1163**.

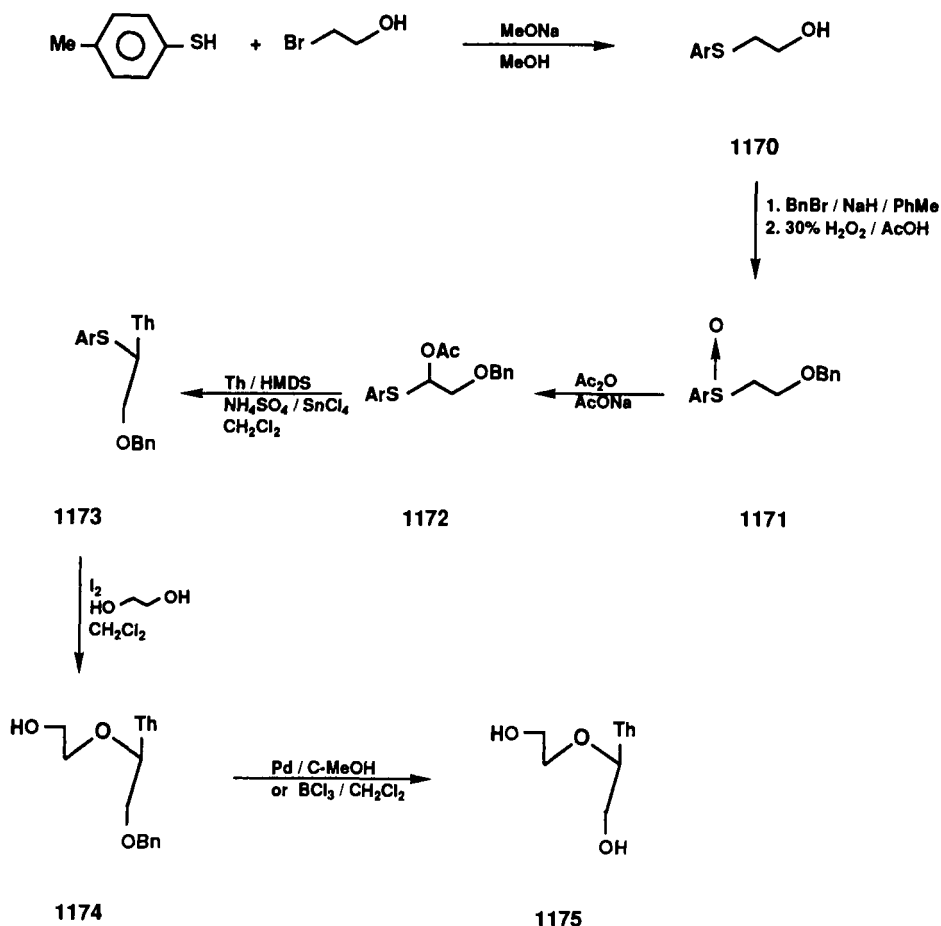
2',3'- and 3',4'-*seco*-Nucleosides of type 1.2 carrying fluorine and sulfur substituents at C-3' and C-5', respectively, were synthesized in enantiomerically and diastereoisomerically pure form (93FA1113).

2',3'- and 3',4'-*seco*-Nucleosides of types 1.2 and 1.3 were prepared from **1164** by protection as the silyl derivative **1165**, whose periodate oxidation and subsequent reduction gave **1166**, which was deprotected to give **1167**. Methoxytritylation and desilylation of **1165** gave **1168**, which, upon periodate oxidation, reduction, and deprotection, gave **1169** [94BSF118, 94JCS(P1)1289].

The stereospecific synthesis of 3',4'-*seco*-nucleosides of guanosine and its 2'-deoxy analog of type 1.3 used ring opening of suitably protected 9- $\alpha$ -L-arabinopyranosylguanines (92BMC667). The thymine analog of type 2.3 was prepared by a synthetic strategy involving a key step in which the C-1'-substituted tolylthio intermediate **1173** was activated with iodine in the presence of ethylene glycol to give the *diseco*-nucleosides **1174**, then deprotected to give **1175**. The intermediate **1173** was prepared from *p*-



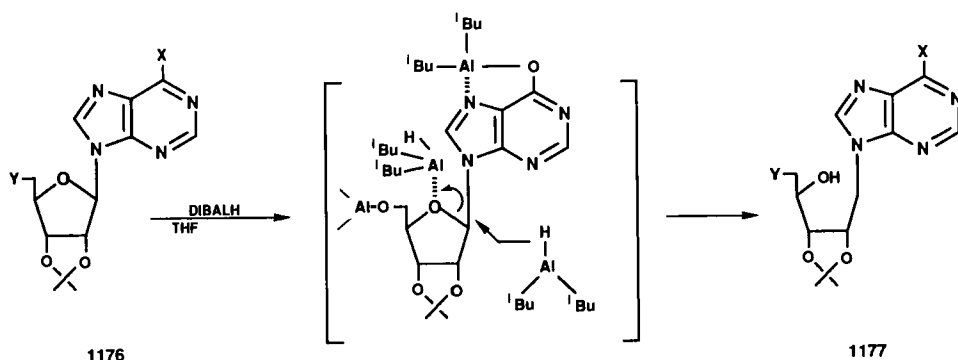
SCHEME 229



SCHEME 230

thiocresol by alkylation with 2-bromoethanol to give **1170**, protected as a benzyl derivative. The sulfide moiety was oxidized to the sulfoxide **1171**; Pummerer rearrangement gave **1172**, which was coupled with thymine to give the required intermediate **1173** (93MI13). The nucleosides were not active against HSV-1, HZV, or HCMV.

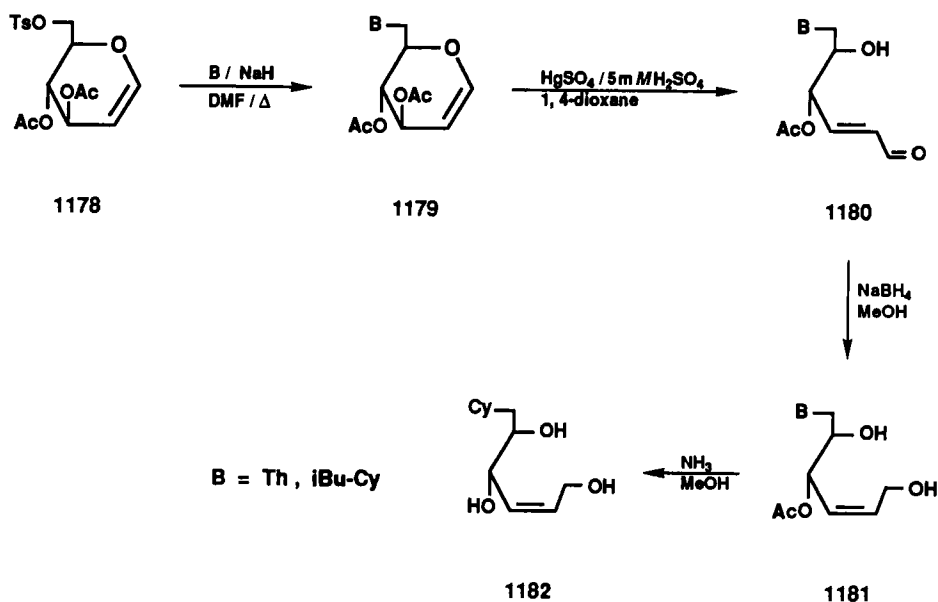
Purine nucleosides of type 1.4 (**1177**) were prepared by the reductive cleavage at the anomeric position of the ribofuranosyl moiety of **1176** with diisobutylaluminum hydride (DIBALH). The reductive ring opening was explained by the initial formation of a Lewis complex (93TL4835).



SCHEME 231

Modified thymine and cytosine analogs of type 1.4 were also prepared by the ring-opening of the D-glucal derivative **1179**, obtained from **1178**, to give **1180**, which upon reduction gave **1181**. Deprotection of the cytosine derivative gave **1182** (93ACS889).

2',3'-Dideoxy analogs of type 1.4 were prepared by alkylation of the pyrimidine bases with the tosylate **1183** to give **1184**, whose hydroxylation gave **1185**; its epoxidation, however, gave **1187**, whose epoxide ring opening



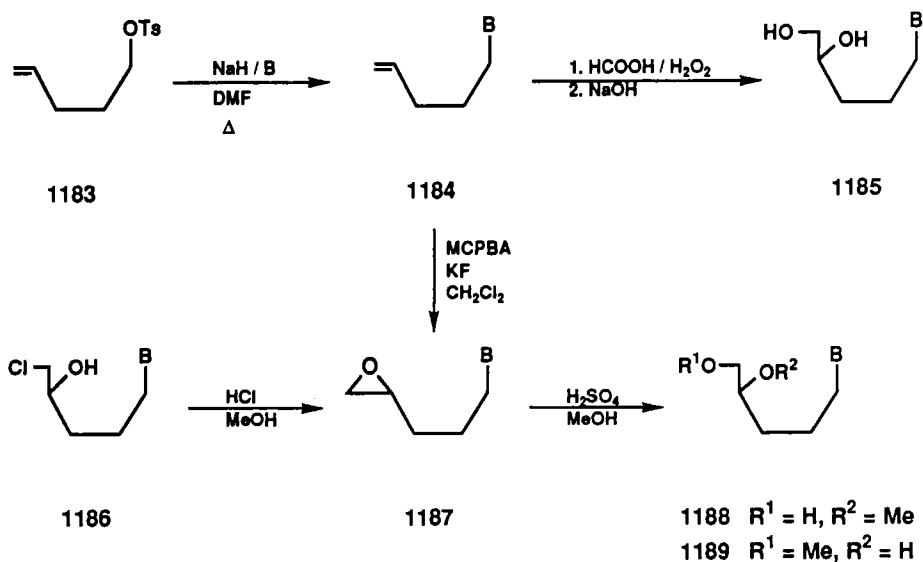
SCHEME 232

gave **1186** and **1188** or **1189** (93ACS889). The synthesis of *cis*-2-pentene-containing nucleoside analogs was reported (93MI6).

Addition of a catalyst containing sulfuric acid and acetic anhydride to 3',5'-di-*O*-acetylthymidine in acetonitrile results in an equilibrium mixture of  $\alpha$ - and  $\beta$ -anomers that, after time, gave a substantial quantity of a diastereoisomeric mixture of fully acetylated open-chain nucleosides. These were of type 1.5 with 2'-deoxy and 4'-acetoxy substituents (93TL6779). Open-chain nucleoside was also obtained as well as the expected nucleoside when 5-nitouracil was condensed with methyl-2,3-dideoxy-3-fluoro-5-*O*-(4-phenylbenzoyl)- $\beta$ -D-*erythro*-pentofuranoside (94S516).

A series of *C*-nucleoside analogs of type 1.5 were prepared from the reaction of 1-bromodeoxyheptulose derivatives with 3-arylamino-2-cyano-3-mercaptoacrylic acid ethyl ester, 3-amino-5-thioxopyrazolin-4-carboxylic acid ethyl ester, and 2-amino-4-thioxo-4,5-dihydro-1*H*-benzo[*b*][1,4]-diazepin-3-carboxylic acid ethyl ester (86PHA548).

Several thymine analogs of type 2.1 were prepared from 1-benzyloxypropylene oxide by azidolysis followed by chloromethylation to give **1190**, which could be transformed to **1191**. Both **1190** and **1191** could be used for coupling to give **1192**, which could be transformed to **1193** or the HEPT analog **1196** (94S939). More HEPT analogs of type 2.1 were also prepared. Azapyrimidine analogs of **1193** were converted to the urea derivatives,

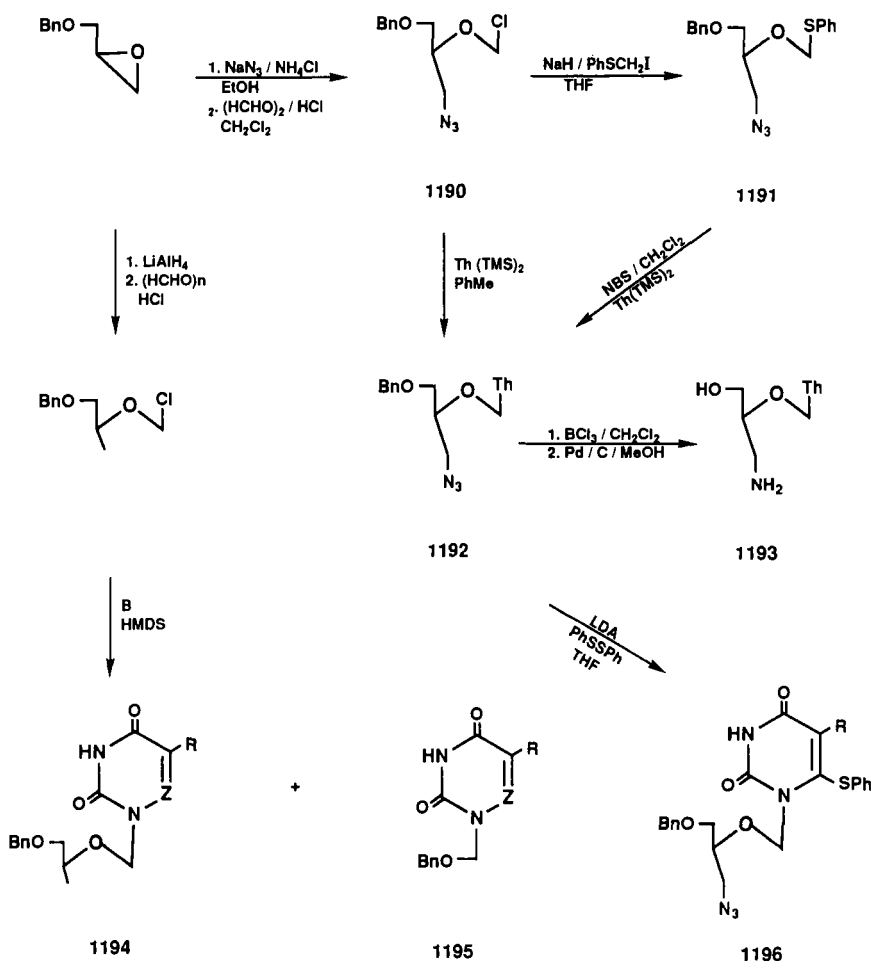


SCHEME 233

whose nitrosation gave both of the nitrourea derivatives (93MI4). They were inactive against HeLa and KB human carcinoma cells.

The deoxy analogs of 2.1 were prepared by coupling 1-benzyloxy-2-chloromethoxypropane with silylated thymine, 6-azathymine, uracil, and 6-azauracil to give the anticipated nucleosides **1194** in addition to minor quantities of benzyloxymethylated produce **1195** of type 5.1 (94MI15). None of the deprotected nucleosides exhibited significant activity against HIV.

The 2-amino-7-substituted purine of type 2.1 is a potent and selective inhibitor of herpes replication (94AAC2710; 95AAC56).



SCHEME 234

Regiospecific ring opening of several alkoxy-1,4-diheterocycloheptanes **1197** with several silylated 5-substituted pyrimidine bases provided acyclic nucleosides **1198** (93SL389). The antitumor activity of the acyclic nucleosides was studied.

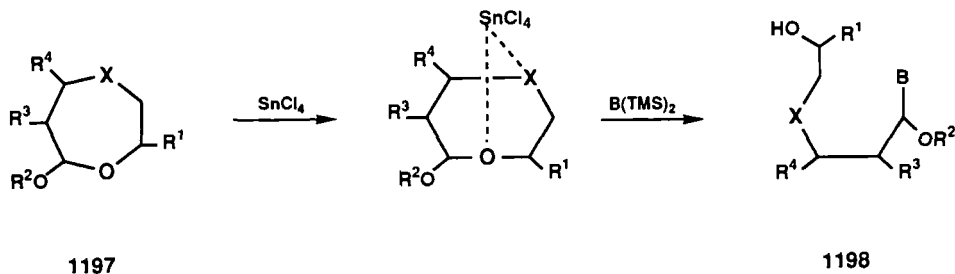
Analogues of type 3.1 or type 2.2 with translocation of the oxygen and carbon atoms were prepared by a coupling method whereby a (2-hydroxyethoxy)ethyl moiety is attached to uracil, cytosine, and adenine (94MI19). 5-Halogenated derivatives of uracil and both the 7- and 9-isomers of adenine were also prepared. Only the guanine derivative displayed marginal activity without any apparent cytotoxicity against HSV-1 (93MI3).

The reaction of 1-deoxy-1-isothiocyante-D-fructose with carbon disulfide was dependent on the conditions whereby acyclic nucleosides of type 2.7 (**1199**) or **1200** could be formed. The latter was rearranged to **1201** by the action of acid (94MI8).

The synthesis of cytallene and 5-fluorocytallene were carried out by the alkylation of the respective cytosine with 1-benzoyloxy-4-bromo-2-butyne followed by debenzoylation, transformation to the *N*-4-dimethylaminomethylene derivative, and, in the case of the fluoro analog, isomerization to the allene and then deprotection (94MI18; 95JMC1397). Suppression of the infectivity and replication of HIV-1 was shown. Unsaturated acyclic analogs of type 2.7 or 3.4 having fluorobutynol and fluorobutanol residues were prepared by alkylation with bromofluorobutyne or by reaction of the ethanol derivatives of the base with (carbethoxyfluoromethyl)triphenylphosphonium bromide followed by reduction (92MI1; 95JMC875). The biological activity of the different isomeric derivatives was studied.

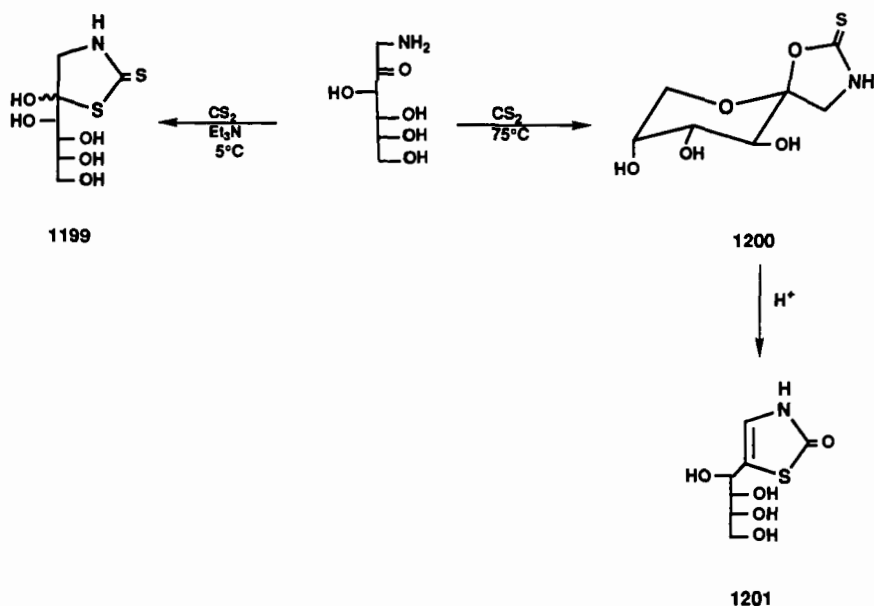
6-Fluoropurines of types 2.1 and 3.1 were found to be more efficiently metabolized to acyclovir and ganciclovir by adenosine deaminase than the corresponding 6-aminopurine analogs (94AAC2710).

The synthesis of 1-[1,3-dihydroxy-2-propoxy)methyl]-6-azaisocytosine (type 2.1) and the respective 3.1 type was achieved by the coupling method.



SCHEME 235

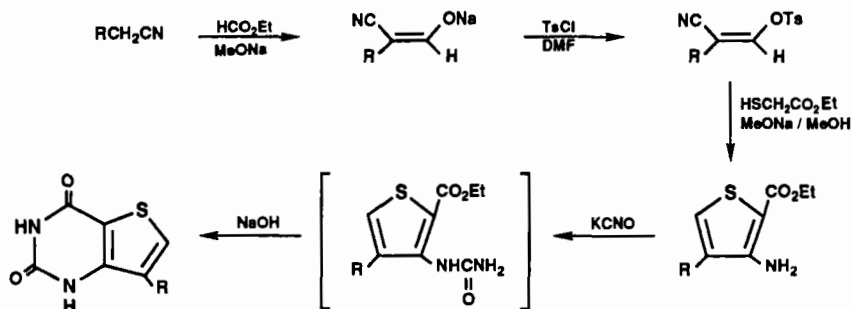




SCHEME 236

An X-ray structure of the latter was reported (95H293). None of them was active against HSV-1 or HSV-2.

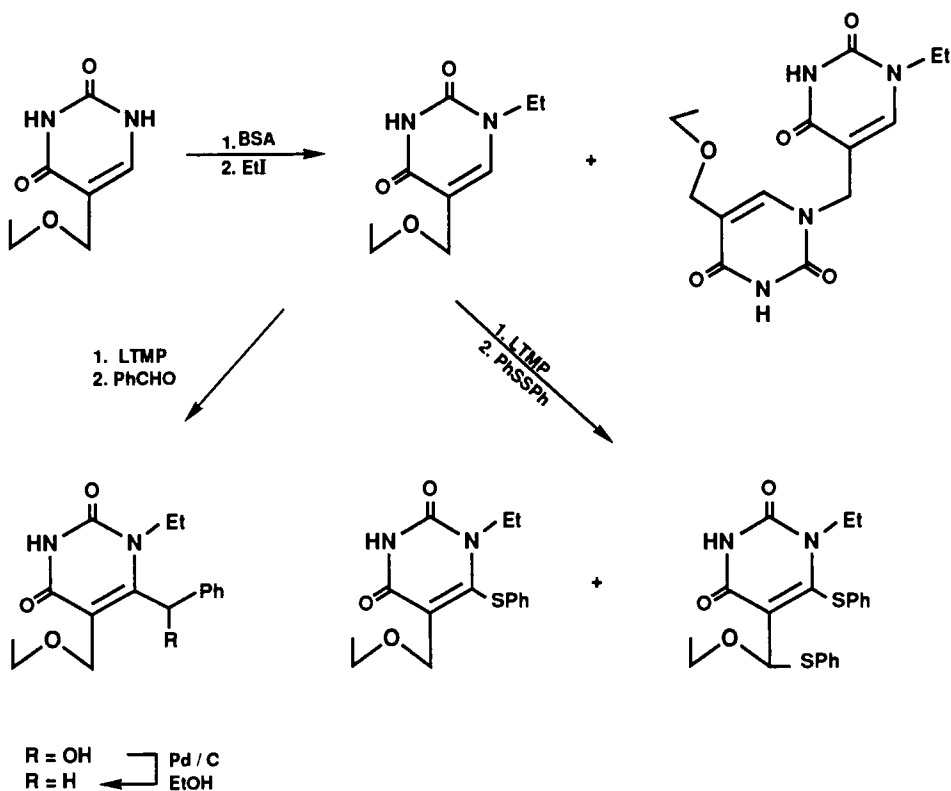
The thieno[3,2-*d*]pyrimidine-2,4-diones were prepared as shown in Scheme 237, and their silyl derivatives were coupled with various acetoxy-methyl ethers in the presence of stannic chloride to give *diseco* (type 2.1), *triseco* (type 3.1), and *pentaseco* benzyl derivatives of type 5.1 nucleosides (94JHC305).



SCHEME 237

Analogues with a saturated thiophene ring were also prepared (94MI14) and conversion to their azido derivatives examined using  $\text{Ph}_3\text{P}/\text{Cl}_4/\text{NaN}_3$  (94MI12). None of them showed any significant activity against HIV-1.

A number of papers were published on nucleosides of type 3.1. The details of a one-pot synthesis of acyclonucleosides of type 3.1 were reported as treatment of the silylpyrimidine bases directly with 1,3-dioxolane or 2-methyl-1,3-dioxolane, chlorotrimethylsilane, and a metal iodide in acetonitrile at room temperature (92MI2; 95CPB142). The acyclovir and ganciclovir derivatives were prepared by the *trans*-glycosylation method (93EUP532878). The conversion of guanosine into acyclovir and its 6-deoxy derivative was achieved (94T9195) by the reaction of the ribofuranosyl 6-chloropurine derivative with 4-chloro(thiophenol) followed by hydrolysis. The respective base was alkylated with acetoxyethoxymethyl bromide to give an acyclic nucleoside of type 3.1 that could be converted to acyclovir and its analogs.

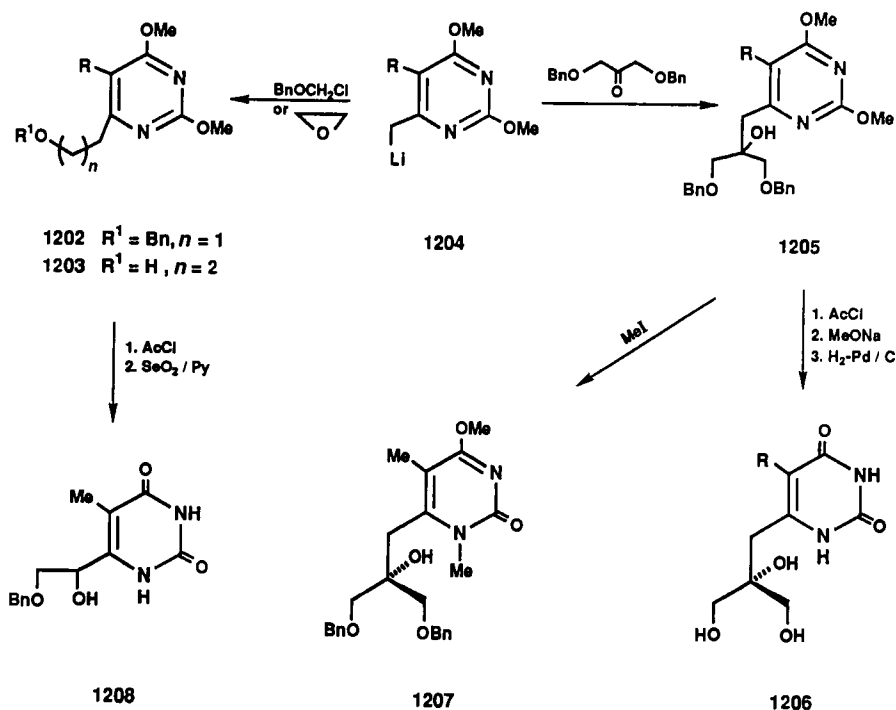


SCHEME 238

6-Methylidene-9-purine analogs were prepared by the reaction of 6-chloropurines with active methylene compounds (94PHA480). A 5-trifluoromethanesulfonylpyrimidine of type 3.1 was prepared (93T5873).

Carbohydrate derivatives of acyclovir were prepared as potential pro-drugs (94MI1). The synthesis of 2-aminopurine derivatives of type 3.1 started with the corresponding guanine-6-arenesulfonates (94MI11). Analogs of type 3.1 were prepared that have imidazole, imidazo[4,5-*d*][1,3]thiazine-7-thione (93JAP(K)05/163282], 2-(trifluoromethylthiomethyl) benzimidazole (89KGS493), indole, benzotriazole (92MI4), cyclopentano [*d*]pyrimidine-2,4-dione and octahydroquinazoline-2,4-dione (94MI13), lumazine (93MI14), and 2-nitroimidazole (93JHC1351). The radiolabeling and biodistribution of the last analog was studied. Acyclic glycosylation of thiadiazine gave the diacyclonucleoside analog, whose regioselective lipase-mediated acylation-deacetylation was studied (94T13865).

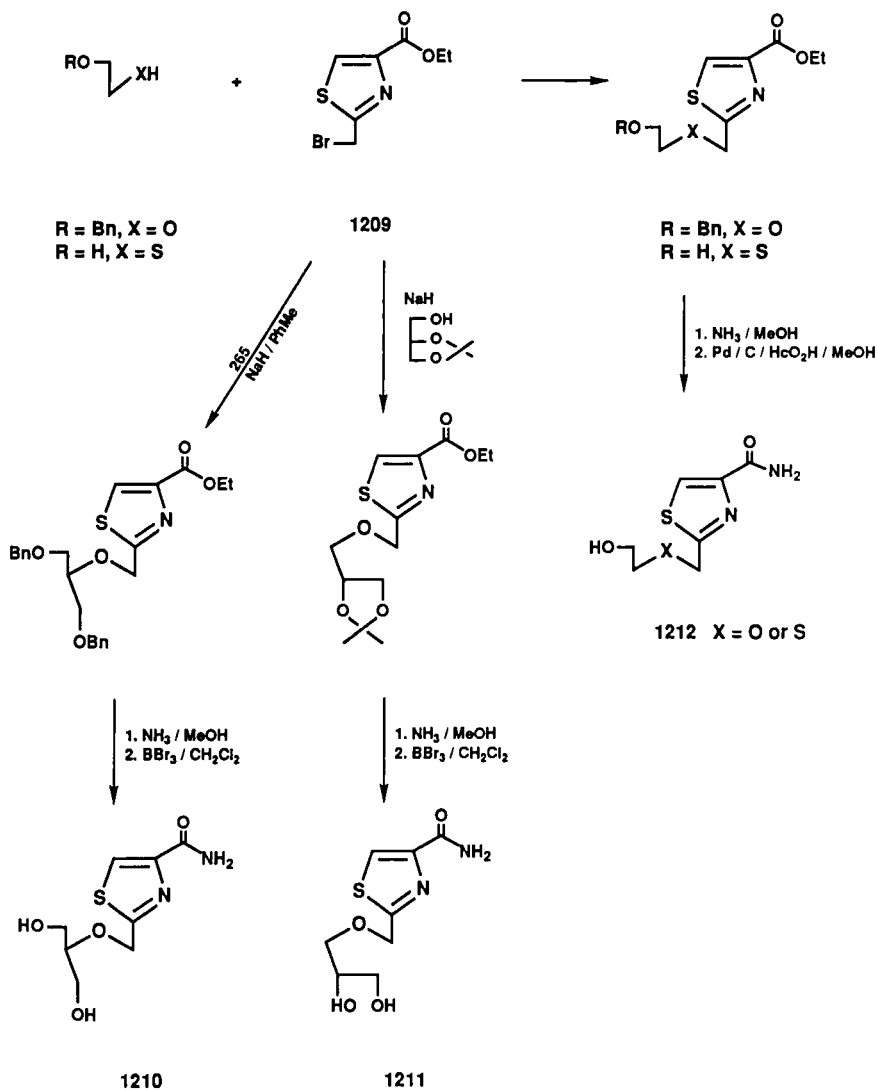
Acyclic *C*-nucleoside analogs of imidazo[1,2-*a*]pyrimidine analogs were prepared (95MI2). Regioisomeric analogs of HEPT were prepared as shown in Scheme 238 (94MI9) and possessed activity against HIV-1.



SCHEME 239

Ring-opened analogs of pyrimidines such as 6-(4-hydroxybutylamino)-pyrimidines were reported (94JMC3057; 94MI17).

Acyclic *C*-nucleoside analogs of type 4.3 (**1203** and **1205**) were made from the lithiated 2,4-dimethoxy-5,6-dimethylpyrimidine (**1204**) (94MI10). Treatment with acetyl chloride caused the hydrolysis of the OMe groups.



SCHEME 240

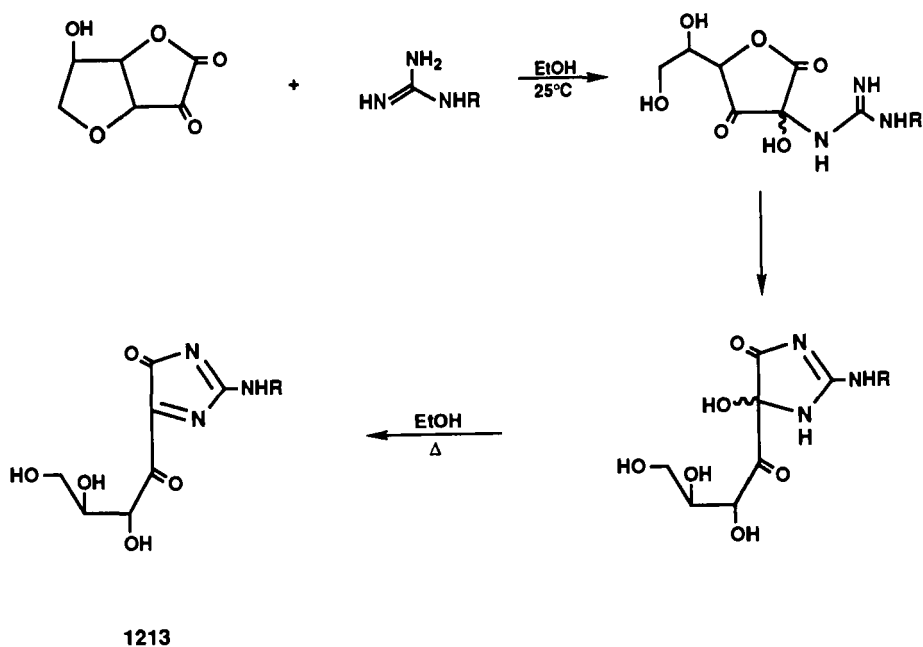
Treatment of **1205** with MeI gave **1207**. Oxidation of the demethylated derivative of **1202** with SeO<sub>2</sub> gave **1208**. None of the compounds were active against viruses or HIV.

Acyclic C-nucleoside analogs of tiazofurin have been synthesized by using ethyl 2-bromomethylthiazole-4-carboxylate (**1209**) as a key intermediate (95PC1). Thus, analogs of the *diseco* and *triseco*-nucleosides of types **1210**, **1211**, and **1212** were prepared as shown in Scheme 240. None of them was active against L<sub>1210</sub> leukemia or herpes simplex type 1 (HSV-1).

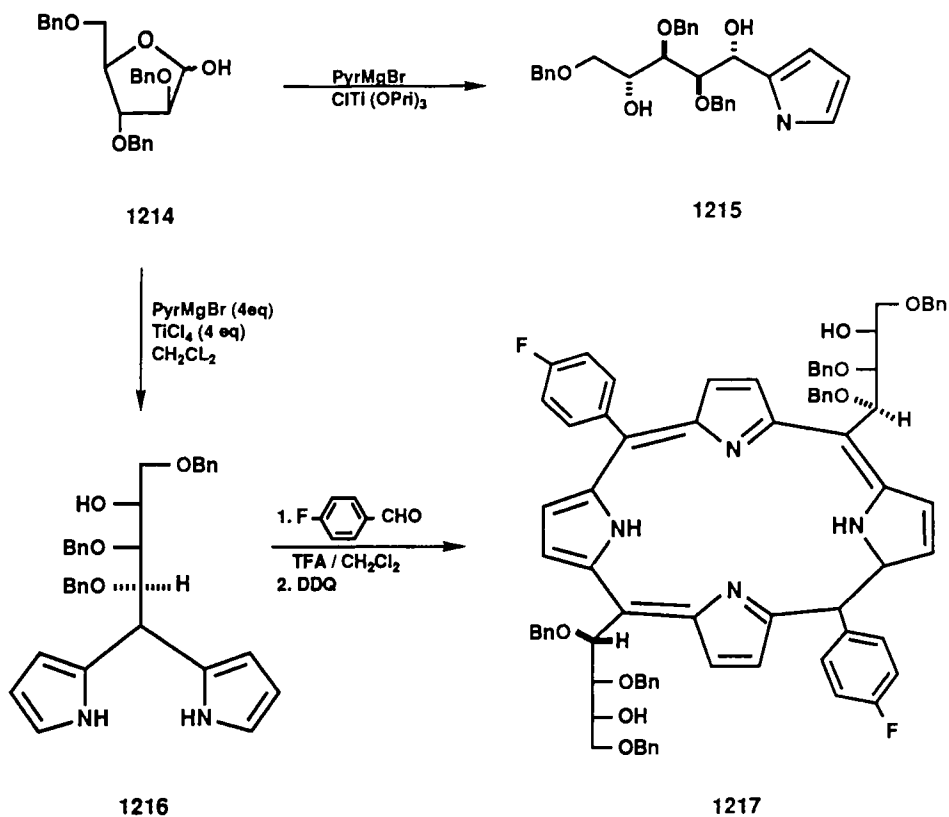
Acyclo-C-nucleoside analogs possessing oxazole rings were obtained from the rearrangement of lactoxime *o*-vinyl ethers or sugar lactoxime *o*-vinyl ethers [92JCS(P1)2127]. In some cases, epimerization took place at the C-2 position.

Reaction of dehydro-*L*-ascorbic acid with guanidine derivatives gave the 2-aminoimidazole acyclo-C-nucleoside analog **1213**, as shown in Scheme 241 (92T6385).

Enantiomerically pure open-chain  $\alpha$ -pyrrylalдитols such as C-nucleoside analogs **1215** have been synthesized by direct coupling of sugar derivatives **1214** with pyrrole metal reagents based on magnesium–titanium<sup>IV</sup> or mag-



SCHEME 241



SCHEME 242

nesium–cerium blends. The dinuclear compound **1216** is a precursor of the sugar porphyrin **1217** (92T5619).

Analogues of type 4.3 were prepared from 3-deaza-adenine, 3-deazapurine, 1-deaza-adenine, pyrimidines, and 4-amino-6-bromo-5-cyanopyrrolo[2,3-*d*]pyrimidine (93CCC629; 93CCC649). The critadenine analogue was prepared from the reaction of 2,3-*O*-cyclohexylidene-D-erythronolactone with 3-deaza-adenine. Some deaza-adenine derivatives exhibit SAHase activity. Allylation of pyrimidine derivatives followed by hydroxylation gave analogues of type 4.3 (93CCC2955; 94CCC683), which were evaluated against Ranikhet disease virus. Analogues of types 5.1 and 5.2 were prepared in the pyrimidine series and their biological activity was evaluated (94MI3, 94MI6).

## ACKNOWLEDGMENT

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# Conformational Analysis of Saturated Six-Membered Oxygen-Containing Heterocyclic Rings

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## I. Introduction

This article deals with the conformational analysis of substituted oxanes (tetrahydropyranes) and derivatives in which ring methylenes are replaced by further oxygen atoms (di-, tri-, tetroxanes, pentoxanes, and O<sub>6</sub>) or by carbonyl group(s) (oxanones, Meldrum's acid derivatives) and, if conformationally of interest, systems incorporating these rings in polycyclic structures

(see Fig. 1). Also, the deprotonated 1,3-dioxan-2-ylum salts and oxanylmethyl radicals are included as far as their conformation was studied. The present review is based on the pertinent literature up to 1995.

A comprehensive review on this topic has not yet been published, although a number of review articles by Eliel (70ACR1; 72AG779; 73CZ582; 75JCE762), Lambert (75CRV611) and Riddell's book (80MI), dealing with the conformational analysis of six-membered saturated heterocyclic compounds as a whole, and the review of Anteunis (76H293), covering the conformational analysis of 1,3-dioxanes until 1975, constitute relevant previous overviews of this topic.

## II. Methods Used to Determine the Conformation

The best method used in the conformational analysis of saturated six-membered heterocyclic rings in the *solid state* is single-crystal X-ray structural analysis. The conformation in solution is not always identical. For solutions,  $^1\text{H}$  NMR spectroscopic analysis has been employed widely in the field of conformational analysis. The following methods deserve special mention.

1. *Chemical equilibration of conformationally fixed model compounds.* Diastereomeric analogs of the distinct *axial* and *equatorial* conformations

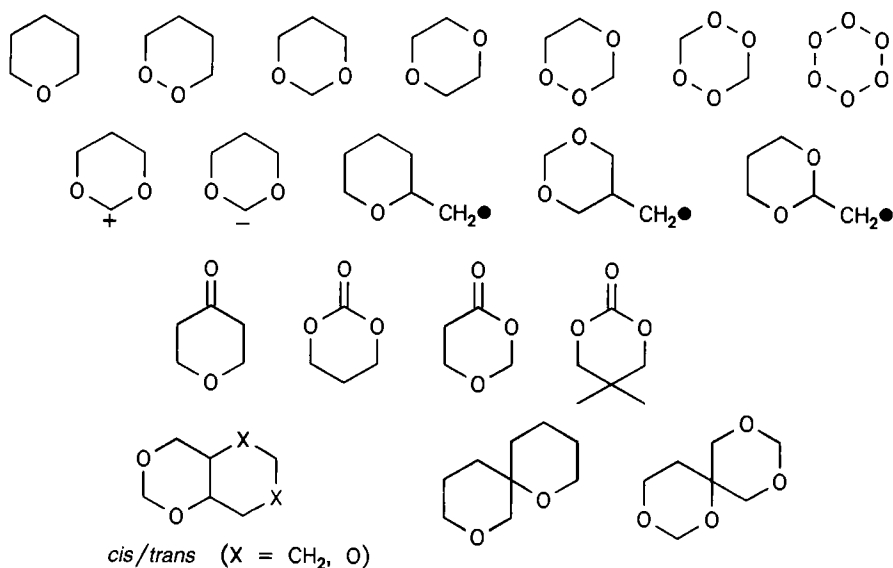


FIG. 1. Conformational analysis of oxane derivatives.

present in a mobile heterocycle are equilibrated (usually by means of acidic or basic catalysis) until identical equilibrium mixtures are obtained. Integration of areas of the appropriate nuclear magnetic resonance (NMR) signals in each isomer affords the equilibrium constant  $K$  and the free energy difference ( $-\Delta G^\circ$ ) of the conformations:

$$K = [\textit{equatorial}]/[\textit{axial}] \quad (1)$$

$$-\Delta G^\circ = RT \ln K \quad (2)$$

2. *Frozen conformational equilibria.* Although the rate of the interconversion of the various conformers (chair, boat, twisted) of the oxane derivatives at ambient temperature is fast on the NMR timescale, this ring-inversion process is sufficiently slow at low temperature ( $T < -60^\circ\text{C}$ ) to permit the observation of individual signals for each conformer. Direct integration delivers  $K$  and  $-\Delta G^\circ$ , respectively [see Eqs. (1) and (2)].

3. *Conformational equilibria still fast on the NMR timescale.* From reference compounds (diastereomeric analogs, e.g., 4-*tert*-butyl or 3,5-*cis*-dimethyl substitution operating as a kind of conformational anchor), the NMR parameters of the purely *equatorial* and *axial* conformers ( $P_{\text{eq}}$  and  $P_{\text{ax}}$ , respectively) can be determined. The equilibrium constant  $K$  [Eq. (3)] from these parameters and that of the population-weighted observed NMR parameter,  $P$ , can be estimated from the fast equilibrium [59CI(L)568]:

$$K = [P_{\text{ax}}] - [P]/[P] - [P_{\text{eq}}] \quad (3)$$

The NMR parameters  $P_{\text{ax}}$  and  $P_{\text{eq}}$  must be sufficiently different in the axial and equatorial conformers to have an accurate measure of  $K$ . The following are most commonly used:

Chemical shifts of magnetically active nuclei, such as  $^{13}\text{C}$  [79MI171],  
Vicinal and geminal scalar H,H and H,C coupling constants  
Line widths of proton resonances of tertiary protons

The methyl-substituent effects on the  $^{17}\text{O}$  chemical shifts in oxanes, 1,3-, and 1,4-dioxanes (79TL3649) and the direct scalar coupling constants in 1,3-dioxanes [ $^1J(\text{C-2}, \text{H-2})$ ,  $^1J(\text{C-2}, \text{C}(\text{Me})\text{-2})$  and  $^1J(\text{C-2}, \text{P-2})$ ] [77TL3573; 78CB3325; 88TL5621; 94JCS(P2)1151] have also been employed for conformational and configurational assignments.

In addition to NMR spectroscopic analysis, ultraviolet (UV), infrared (IR), and photoelectron spectroscopy and dipole moments were partially in use for the estimation of conformational equilibria or the presence of preferred conformers. Even the different reactivity of epimers was used for relevant stereochemical assignments.

The most salient feature of the conformational behavior of substituted oxanes (and also of related systems and also carbohydrates) is that polar substituents X in position 2 prefer the axial orientation as result of the *anomeric effect* (even if this conformation is sterically more hindered). Two alternative origins of the anomeric effect have been suggested: (1) dipole/dipole repulsion in the corresponding equatorial conformer and (2) *hyperconjugative* donation of the ring oxygen lone pair into the antiperiplanar C—X antibonding orbital ( $n_o \rightarrow \sigma^*_{c-x}$ ) in the axial conformer (95MI).

### III. Conformational Analysis

#### A. OXANES

The chair conformation is the preferred conformer for the oxane ring and substituted derivatives. In the case of poly-substitution (e.g., 1,3-diaxial groups), twist conformers can also participate in the equilibrium. Substituents can adopt the axial and equatorial positions; ring interconversion between the chair conformers is fast on the NMR timescale at ambient temperature but becomes slow at low temperature ( $\Delta G^\ddagger = 10.3 \text{ kcal mol}^{-1}$ ) (73JA4634).

The conformational energies of monosubstituted oxanes studied to date are collected in Table I. In position 2, polar substituents (except  $\text{NR}_2$ ) prefer the axial position; other substituents prefer the equatorial orientation, which is generally the case for groups in positions 3 and 4. Destabilizing 1,3-diaxial interactions cause the equatorial geometry to be usually favored; in the 2-position, the anomeric effect stabilizes the axial conformation. A large purine moiety in position 2 of oxane, for example, prefers the equatorial position because the 1,3-diaxial interactions overcome the anomeric effect (75TL1553).

The conformational equilibria of the various substituted oxanes in Table I are strongly dependent on the solvent. The polarity of the solvent and the possibility to form inter- or intramolecular hydrogen bonds are of significant influence (69CJC4427; 87CJC213).

In following the temperature dependence of  $\Delta G^\circ$ , Booth *et al.* [85JC-S(CC)467; 87T4699] also determined  $\Delta H^\circ$  and  $\Delta S^\circ$  for the conformational equilibria of 2-Cl-, 2-OMe-, 2-OH-, and 2-NHMe-oxanes (see Table II) and discussed the results in terms of exo- or endo-anomeric effects (Section III,C,8). Employing the NOE and a number of H,H- and C,H-coupling constants as a means of analysis, the preferred rotamers of axial/equatorial-2-OMe-oxane were found to be in the conformations  $a_2$  and  $e_2$ , respectively, as given in Scheme 1 (90T1525).

TABLE I  
CONFORMATIONAL ENERGIES (FREE ENERGY DIFFERENCES,  $\Delta G^\circ/\text{kcal mol}^{-1}$ ) OF  
SUBSTITUTED OXANES

Substituent	Solvent	$-\Delta G^\circ$	Ref.
2-Cl	CCl <sub>4</sub>	$\leq -1.8$	66JOC544
2-Br	CCl <sub>4</sub>	$\leq -1.8$	66JOC544
2-I	CCl <sub>4</sub>	$\leq -2.6$	67JOC607
2-OMe	CCl <sub>4</sub>	-0.73	68JOC3754
		-0.89	69T3365
	CFCl <sub>3</sub> /CDCl <sub>3</sub> (85:15)	-0.38	84BSB1047
	CDCl <sub>3</sub>	-0.46	87CJC213
2-OEt	CCl <sub>4</sub>	-0.67	68JOC3754
		-0.89	69T3365
2-OCH <sub>2</sub> CF <sub>3</sub>	CCl <sub>4</sub>	-0.83	68JOC3754
2-O- <i>n</i> Pr	CCl <sub>4</sub>	-0.89	69T3365
2-O- <i>i</i> Pr	CCl <sub>4</sub>	-0.64	68JOC3754
		-0.65	69T3365
2-O- <i>n</i> Bu	CCl <sub>4</sub>	-0.89	69T3365
2-O- <i>t</i> Bu	CCl <sub>4</sub>	-0.50	68JOC3754
		-0.41	69T3365
2-OC(Me) <sub>2</sub> C $\equiv$ CH	CCl <sub>4</sub>	-0.54	68JOC3754
2-OCOMe	CCl <sub>4</sub>	-0.6	68CI(L)1805
	CCl <sub>4</sub>	-0.82	70ZOR863
	Acetone	-0.50	74OMR233
2-OPh	Acetone	-0.37	74OMR233
2-OH	CCl <sub>4</sub>	-0.19	74OMR233
2-OD	CDCl <sub>3</sub>	-0.02	87CJC213
2-OCH <sub>2</sub> CF <sub>3</sub>	CDCl <sub>3</sub>	-1.06	87CJC213
2-OCH <sub>2</sub> CH <sub>2</sub> F	CDCl <sub>3</sub>	-0.52	87CJC213
2-OCH <sub>2</sub> CH <sub>2</sub> OAc	CDCl <sub>3</sub>	-0.46	87CJC213
2-OSi(CH <sub>3</sub> ) <sub>3</sub>	CDCl <sub>3</sub>	-0.07	87CJC213
2-OCH <sub>2</sub> CH <sub>2</sub> OD	CDCl <sub>3</sub>	-0.15	87CJC213
2-COOMe	CD <sub>2</sub> Cl <sub>2</sub>	1.38	82JA3635
2-C $\equiv$ CH	CD <sub>2</sub> Cl <sub>2</sub>	0.34	82JA3635
2-CH=CH <sub>2</sub>	CD <sub>2</sub> Cl <sub>2</sub>	2.27	82JA3635
2-CH <sub>2</sub> OH	CD <sub>2</sub> Cl <sub>2</sub>	2.89	82JA3635
2-CH <sub>3</sub>	CD <sub>2</sub> Cl <sub>2</sub>	2.86	82JA3635
	CD <sub>3</sub> OD	1.70	68JOC3272
2-C <sub>2</sub> H <sub>5</sub>	CD <sub>2</sub> Cl <sub>2</sub>	2.62	82JA3635
2-SCH <sub>3</sub>	CCl <sub>4</sub>	-0.35	68JOC3754
2-SEt	CCl <sub>4</sub>	-0.4	70RTC972
2-S- <i>i</i> Pr	CCl <sub>4</sub>	-0.50	74OMR233
2-S- <i>n</i> Pr	CCl <sub>4</sub>	-0.4	70RTC972
2-S- <i>n</i> Bu	CCl <sub>4</sub>	-0.5	70RTC972
2-S- <i>t</i> Bu	CCl <sub>4</sub>	-0.37	68JOC3754
2-NR <sup>a</sup>	CDCl <sub>3</sub>	0.37	75TL1553
	CD <sub>3</sub> CN	0.62	75TL1553
2-N(CH <sub>2</sub> ) <sub>2</sub>	CD <sub>2</sub> Cl <sub>2</sub>	0.56	82JCS(P2)249
2-NHMe	CD <sub>2</sub> Cl <sub>2</sub>	0.9	82JCS(P2)249

(continues)



TABLE I (continued)

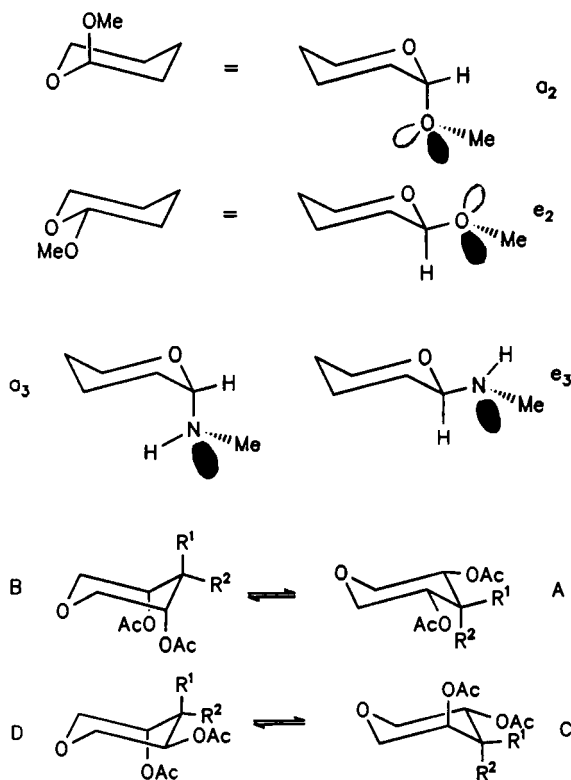
Substituent	Solvent	$-\Delta G^\circ$	Ref.
2-NH- $\beta$ -naphthyl	CD <sub>2</sub> Cl <sub>2</sub>	0.89	82JCS(P2)249
2-NHCOMe	CCl <sub>4</sub>	1.03	70ZOR863
2-N <sub>3</sub>	CCl <sub>4</sub>	-0.82	70ZOR863
2-NCO	CCl <sub>4</sub>	-0.50	70ZOR863
3-OCOMe	CCl <sub>4</sub>	0.17	68Cl(L)1805
3-Cl	CCl <sub>4</sub>	0.68	75T1149
3-Br	CCl <sub>4</sub>	1.0	75T1149
3-Me	CD <sub>2</sub> Cl <sub>2</sub>	0.53	81PJC1265
	CD <sub>2</sub> Cl <sub>2</sub>	1.44	81PJC1265
	CD <sub>2</sub> Cl <sub>2</sub>	1.43	82JA3635
	CD <sub>3</sub> OD	1.27	68JOC3272
3-CH <sub>2</sub> OH	CD <sub>2</sub> Cl <sub>2</sub>	0.78	81PJC1265
3-CHO	CD <sub>2</sub> Cl <sub>2</sub>	0.0	81PJC1265
3-COOMe	CD <sub>2</sub> Cl <sub>2</sub>	0.59	81PJC1265
3-SMe	CD <sub>2</sub> Cl <sub>2</sub>	1.21	87JOC4099
3-SOMe (more polar)	CD <sub>2</sub> Cl <sub>2</sub>	0.10	87JOC4099
3-SOMe (less polar)	CD <sub>2</sub> Cl <sub>2</sub>	0.43	87JOC4099
3-SO <sub>2</sub> Me	CD <sub>2</sub> Cl <sub>2</sub> /CD <sub>3</sub> OD	<1.4	87JOC4099
3-S <sup>+</sup> Me <sub>2</sub> tosylate	CD <sub>2</sub> Cl <sub>2</sub>	-0.55	87JOC4099
3-SH	CD <sub>2</sub> Cl <sub>2</sub>	1.04 <sup>b</sup>	87JOC4099
3-SCH <sub>2</sub> Ph	CD <sub>2</sub> Cl <sub>2</sub>	1.08	87JOC4099
3-SOCH <sub>2</sub> Ph(more polar)	CD <sub>2</sub> Cl <sub>2</sub>	0.07	87JOC4099
3-SOCH <sub>2</sub> Ph(less polar)	CD <sub>2</sub> Cl <sub>2</sub>	0.50	87JOC4099
4-F	CS <sub>2</sub>	-0.05	78SA(A)297
4-Cl	CS <sub>2</sub>	0.31	78SA(A)297
4-Br	CS <sub>2</sub>	0.34	78SA(A)297
4-I	CS <sub>2</sub>	0.44	78SA(A)297
4-OCOMe	CDCl <sub>3</sub>	0.80	73ZC473
4-OMe	CD <sub>2</sub> Cl <sub>2</sub>	0.82	81PJC1265
4-Me	CD <sub>2</sub> Cl <sub>2</sub>	1.95	82JA3635
		1.85	87T4699
	CD <sub>3</sub> OD	1.70	68JOC3272

<sup>a</sup> N-R = 2-substituted (4-Cl-purine).<sup>b</sup> Conformational equilibrium proved strongly concentration dependent.

TABLE II

CONFORMATIONAL ENERGIES [ $-\Delta H^\circ$ ,  $-\Delta G^\circ$  (kcal mol<sup>-1</sup>) AND  $-\Delta S^\circ$  (cal K<sup>-1</sup> mol<sup>-1</sup>)] OF SOME 2-SUBSTITUTED OXANES (87T4699)

Substituent	Solvent	$-\Delta H^\circ$	$-\Delta S^\circ$	$-\Delta G^\circ$
2-Cl	CDCl <sub>3</sub>	-1.67	1.69	-2.18
2-OMe	CFCl <sub>3</sub> /CDCl <sub>3</sub> (85:15)	-0.03	2.52	-0.79
2-OH	CFCl <sub>3</sub> /CDCl <sub>3</sub> (85:15)	0.63	2.50	-0.12
2-NHMe	CFCl <sub>3</sub> /CDCl <sub>3</sub> (85:15)	1.75	0.60	1.57



SCHEME 1

Eliel *et al.* (82JA3635) examined the conformational equilibria of a number of disubstituted oxanes (Table III) by low-temperature  $^{13}\text{C}$  NMR spectroscopy (83OMR94) and estimated the  $\Delta G^\circ$  values of 3-Me and 2-C $\equiv$ CH substituents (see Table I). The concentration of the axial 2-Me and 4-Me conformers, however, was so small and difficult to detect by NMR spectroscopy that they were forced to employ the use of counterpoised *cis*-2-C $\equiv$ CH and *cis*-2-CH=CH<sub>2</sub> groups to generate equilibria that were sufficiently balanced to measure accurately ( $\Delta G^\circ$  values in Table I). Eliel *et al.* (82JA3635) also discussed the conformational energies in terms of 1,3-diaxial interactions and the anomeric effect.

The conformational energies of 2-Me, 3-Me, and 4-Me, respectively, were calculated by Allinger *et al.* (80IJ51) and proved to be in excellent agreement with the experiment.

Alcudia *et al.* [88JCS(P2)1225], in the same way, studied the conformational equilibria of the *cis/trans* isomeric 2-OMe-5-SR-substituted oxanes

TABLE III  
CONFORMATIONAL EQUILIBRIA (FREE ENERGY DIFFERENCES,  $\Delta G^\circ/\text{kcal mol}^{-1}$ )<sup>a</sup> OF  
DISUBSTITUTED OXANES

Compound	Solvent	$-\Delta G^\circ$	Ref.
<i>cis</i> -2,3-di-Me	CD <sub>2</sub> Cl <sub>2</sub>	>1.5	82JA3635
<i>trans</i> -2,4-di-Me	CD <sub>2</sub> Cl <sub>2</sub>	0.89	82JA3635
<i>cis</i> -2,5-di-Me	CD <sub>2</sub> Cl <sub>2</sub>	1.62	82JA3635
<i>cis</i> -3,4-di-Me	CD <sub>2</sub> Cl <sub>2</sub>	0.76	82JA3635
<i>trans</i> -2-COOMe-4-Me	CD <sub>2</sub> Cl <sub>2</sub>	-0.56	82JA3635
<i>cis</i> -2-COOMe-5-Me	CD <sub>2</sub> Cl <sub>2</sub>	0.05	82JA3635
<i>cis</i> -2-C≡CH-5-Me	CD <sub>2</sub> Cl <sub>2</sub>	1.08	82JA3635
<i>trans</i> -2-CH=CH <sub>2</sub> -4-Me	CD <sub>2</sub> Cl <sub>2</sub>	0.32	82JA3635
<i>cis</i> -2-CH=CH <sub>2</sub> -5-Me	CD <sub>2</sub> Cl <sub>2</sub>	0.84	82JA3635
<i>trans</i> -2-CH=CH <sub>2</sub> -6-Me	CD <sub>2</sub> Cl <sub>2</sub>	0.42	82JA3635
<i>trans</i> -2-CH <sub>2</sub> OH-6-Me	CD <sub>2</sub> Cl <sub>2</sub>	0.03	82JA3635
<i>trans</i> -2-Et-6-Me	CD <sub>2</sub> Cl <sub>2</sub>	0.24	82JA3635
<i>trans</i> -2-OMe-5-SMe	CD <sub>2</sub> Cl <sub>2</sub>	0.61	88JCS(P2)1225
<i>trans</i> -2-OMe-5-SOMe(2 $\alpha$ ) <sup>b</sup>	CD <sub>2</sub> Cl <sub>2</sub>	-0.65	88JCS(P2)1225
<i>trans</i> -2-OMe-5-SOMe(2 $\beta$ ) <sup>b</sup>	CD <sub>2</sub> Cl <sub>2</sub>	-0.57	88JCS(P2)1225
<i>trans</i> -2-OMe-5-SO <sub>2</sub> Me	CD <sub>2</sub> Cl <sub>2</sub>	0.50	88JCS(P2)1225
<i>trans</i> -2-OMe-5-S <sup>+</sup> Me <sub>2</sub>	CD <sub>2</sub> Cl <sub>2</sub> /CD <sub>3</sub> OD	$\leq -1.4$	88JCS(P2)1225
<i>trans</i> -2-P(O)OMe <sub>2</sub> -6-CH <sub>2</sub> OAc <sup>c</sup>	CDCl <sub>3</sub>	-0.26	78CB3325

<sup>a</sup> Positive sign means diequatorial conformer preferred.

<sup>b</sup> Diastereotopic sulfoxides found.

<sup>c</sup> In favor of the 2-*ax*-6-*eq* conformer.

(SR = SMe, SOMe, SO<sub>2</sub>Me, S<sup>+</sup>Me<sub>2</sub>; see Table III) and found the *cis* isomers only in the 2-*ax*-5-*eq* conformation. In the *trans* isomers, due to the anomeric effect of both groups, the 2,5-diaxial conformation was found to be populated (see Table III). The *cis/trans* isomer ratios of 2-Me-5-SR-oxane derivatives (SR = SMe, SOMe, SO<sub>2</sub>Me, S<sup>+</sup>Me<sub>2</sub>) (87JOC4099) demonstrated similarly one-sided conformational equilibria (*cis* isomers: 2-*eq*-5-*ax*; *trans* isomer: 2-*eq*-5-*eq*). The conformational equilibria and those of the identically 3-SR monosubstituted oxanes (see Table I) were discussed in terms of the anomeric effect and *gauche* sulfur/oxygen interactions [87JOC4099; 88JCS(P2)1225].

Considering also the <sup>13</sup>C chemical shift of C-2 of a number of 2-substituted oxanes (2-R = -Me, -CH=CMe<sub>2</sub>, -CHMe-CMe=CH<sub>2</sub>, -CH<sub>2</sub>-C-Me=CH<sub>2</sub>) and the shifts of the corresponding *cis/trans* isomeric 2-R-4-Me oxanes, the preferred conformers (2-monosubstituted: 2-*eq*; 2,4-*cis*: 2,4-di-*eq*; 2,4-*trans*: 2-*eq*-4-*ax*) could be readily assigned (78JPR303). In the same way, but additionally employing H,H-coupling constants, the preferred

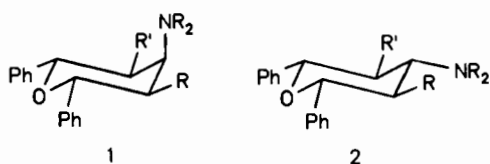
conformation of a number of *cis/trans* isomeric 3,4,4,5-tetrasubstituted oxanes were assigned (see Scheme 1:  $R_1, R_2 = \text{CN}, \text{COOEt}, \text{Boc}, \text{CONH}_2, \text{COMe}$ ) (92T6839). The *cis*-isomers prefer conformer A, but the *trans* isomers adopt both conformers D and C with a small preponderance of conformer C.

Barby *et al.* [82JCS(P2)249] investigated the conformational equilibria of 2-NR<sub>2</sub>-substituted oxanes. The *cis/trans* isomeric 2-NR<sub>2</sub>-4-Me-derivatives proved to adopt preferred conformations (*cis* isomers: 2-*eq*-4-*eq*; *trans* isomers: 2-*ax*-4-*eq*, except for *trans*-2-NHMe-4-Me-oxane preferring the 2-*ax*-4-*eq* conformer by only 0.4 kcal mol<sup>-1</sup>); the 2-NR<sub>2</sub> monosubstituted oxanes (see Table I) prefer the equatorial position and do not show notable anomeric interaction with the ring oxygen atom [82JCS(P2)249]. The same is true for 2-NHCOMe-oxane, but not for N<sub>3</sub> and NCO substituents, respectively, in the 2-position (70ZOR863) (see Table I).

The conformational energies of some 2-monosubstituted oxanes were computed by quantum chemistry at the HF/6-31G\* level (94JOC2138); the results, generally, are in good agreement with experiment and corroborate not only the strongly preferred axial position of 2-OH, 2-OMe, 2-F, and 2-Cl, but also the preferred equatorial arrangement of 2-Me and 2-NH<sub>2</sub>. The preferred equatorial position of 2-NR<sub>2</sub> substituents was corroborated by the MM2 force field (93JCC944); simultaneously, the preferred rotamers *a*<sub>3</sub> and *e*<sub>3</sub> in Scheme 1 of the axial/equatorial 2-NR<sub>2</sub>-oxanes were determined and found to be in complete agreement with the experiment (90T1525). However, the AM1 method failed to calculate accurate conformational energies of 2-substituted oxanes [91JCR(S)6].

Anderson and Sepp (68JOC3272) equilibrated some *cis/trans* isomeric 2-OR-4-Me-, 2-OR-6-Me-, and 2-OR-6-CH<sub>2</sub>OH-oxanes and discussed their equilibria in terms of anomeric interactions. The corresponding conformational equilibria were assumed to be strongly one sided [e.g., the 2,4-isomers: *cis* isomer (2-*eq*-4-*ax*); *trans* isomer (2-*ax*-4-*eq*)].

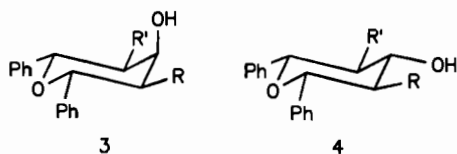
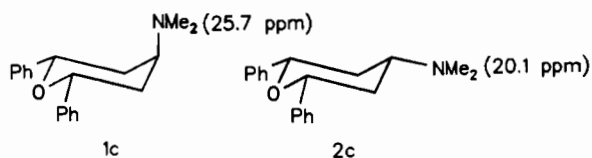
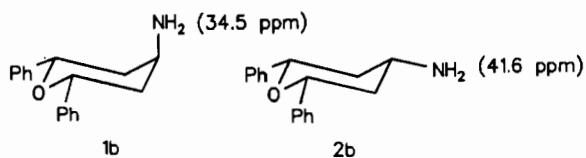
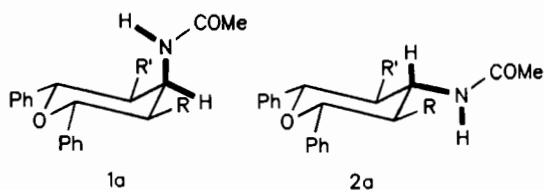
The <sup>1</sup>H and <sup>13</sup>C NMR spectra of the epimers of 2,6-diphenyl-4-NR<sub>2</sub>-oxanes **1** and **2** (Scheme 2) were studied with respect to their preferred conformation [83IJC(B)374, 83JOC1591]. The isomers **1** with the axial NR<sub>2</sub> group in position 4 proved to adopt the chair conformation with the two bulky phenyl substituents in the equatorial position [83IJC(B)374, 83JOC1591] (Scheme 2). In the case of the other isomer with the equatorial NR<sub>2</sub> group, the chair conformer also proved to be preferred; however, when the NR<sub>2</sub> substituent is more bulky (NR<sub>2</sub> = NMe<sub>2</sub>, NMe<sub>3</sub><sup>+</sup>Cl<sup>-</sup>), a number of twist conformations (rapidly interconverting) also participate (83JOC1591). The NH proton in the 4-(acetylamino)oxane isomers **1a, 2a** is *trans* to the proton in position 4, whether axial or equatorial (<sup>3</sup>J<sub>NH,H-4</sub> ca. 7–10 Hz) [83IJC(B)374].



$R, R' = H, \text{Alk}$

$\text{NR}_2 = \text{NH}_2, \text{NHCOCH}_3, \text{NHC(O)H}, \text{NHCH}_3, \text{NH}_3^+\text{Cl}^-$ ,

$\text{NMe}_2, \text{NMe}_3^+\text{Cl}^-, \text{NH-Aryl}$



$R, R' = H, \text{Alk}$

$R, R' = H, \text{Alk}$

SCHEME 2

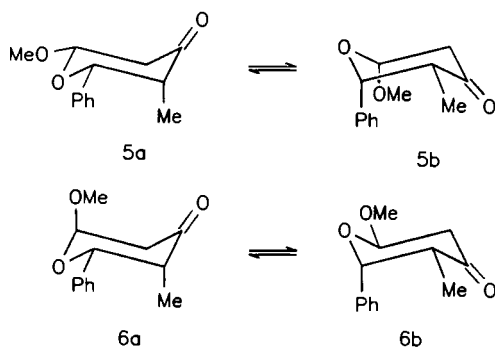
The  $\lambda_{\max}$  values in the UV spectra of the two isomers **1** and **2** [ $R, R' = H$ ;  $NR_2 = N(Me)-C_6H_3(2',4'-di-NO_2)$ ] were at the same wavelength, but for **2** (equatorial  $NR_2$ ) with a higher intensity, a larger steric hindrance in the conjugated moiety was suggested [83IJC(B)410].

The  $^{15}N$  NMR chemical shifts of the axial/equatorial nitrogen atoms in isomers **1** and **2** ( $R = R' = H$ ;  $NR_2 = NH_2, NMe_2$ ) proved useful for conformational analysis (**1b**, **2b**) (82JOC1933). In case of  $NR_2 = NMe_2$ , the chemical shift sequence is reversed (**1c**, **2c** in Scheme 2) (82JOC1933).

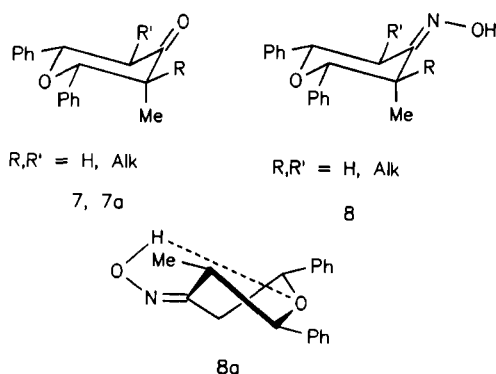
The conformations of the isomeric 4-hydroxy-oxanes **3,4** (Scheme 2) were analyzed on the basis of their rates of oxidation [85JCS(P2)311, 85JCS(P2)1183; 86IJC(B)390]. Contrary to general expectations, the axial alcohols **3** reacted more slowly than the corresponding isomers with the equatorial hydroxy group **4** [85JCS(P2)311, 85JCS(P2)1183; 86IJC(B)390]. One reason for the anomaly is the presence of nonchair conformers in the conformational equilibrium of **3** [85JCS(P2)1183] (as also observed for the corresponding isomeric 4-acetyloxanes [84IJC(B)441]).

The conformation of some oxan-4-ones was also studied. Gung *et al.* (94JOC4895) investigated by variable temperature NMR spectroscopy the conformational equilibrium of *r*-2-Ph,*cis*-3-OMe,*cis*-6-Me-oxan-4-one and found the 2,6-diequatorial conformation **5a** (Scheme 3) to be more stable by ca. 0.3 kcal mol<sup>-1</sup>; the corresponding *trans* isomer prefers the conformer with the methoxy group in axial position **6a** (94JOC4895). MM2 force-field calculations (93JOC1367) and *ab initio* calculations (HF/6-31G\*) (94JOC4899) corroborate the experimental result.

The  $^1H$  and  $^{13}C$  NMR spectra of a number of 2,6-diphenyl-oxan-4-ones **7** and their oximes **8** (Scheme 4) were studied (80JOC4352; 81SPL11). Whereas the oxan-4-ones were in the chair conformation **7a**, the oximes



SCHEME 3



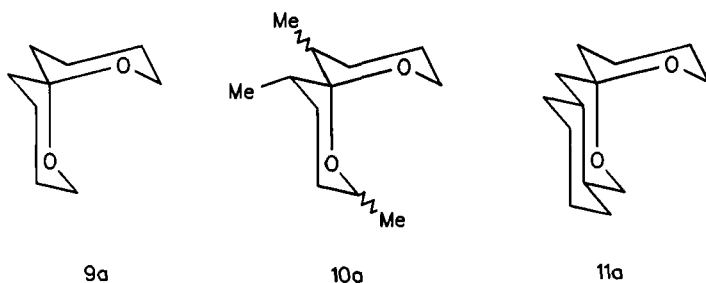
SCHEME 4

preferred the twist-boat conformation **8a** (Scheme 4); both minimization of ring strain and hydrogen bonding between the OH and ring oxygen were found to stabilize **8a**.

The conformation of two 4-phenylsulfonyl-tetrahydropyran-2-one derivatives both in solution and in the solid state was studied (95JPO747); the tetrahydropyran-2-one ring proved to adopt a skew-boat conformation.

The conformations of spiro-compounds containing the oxane ring have been reported (Scheme 5) (81CJC1132). They exist only in conformation **9a** at room temperature; at lower temperature, no indication of a second conformer was found. The methyl-substituted derivatives **10a** and similar tricyclic analogs occur in the same conformation **11a**.

The configuration and conformation of 1-, 3-, 4-, 1,3-, 1,4-, 3,4-, and 1,3,4-methyl-substituted isochromanes were assigned by a combination of  $^{13}\text{C}$  chemical shifts and vicinal H,H coupling constants (85MRC754). The



SCHEME 5

1-methyl ( $-\Delta G^\circ = 0.93 \text{ kcal mol}^{-1}$ ) and 3-methyl derivatives ( $-\Delta G^\circ = 2.05 \text{ kcal mol}^{-1}$ ) prefer the pseudo-equatorial and equatorial positions; the 4-methyl derivative of isochromane in half-chair conformation, however, prefers the pseudo-axial conformation ( $-\Delta G^\circ = -0.43 \text{ kcal mol}^{-1}$ ) (85MRC754). MMP2 force-field calculations completely confirm the experimental results (89JCC407).

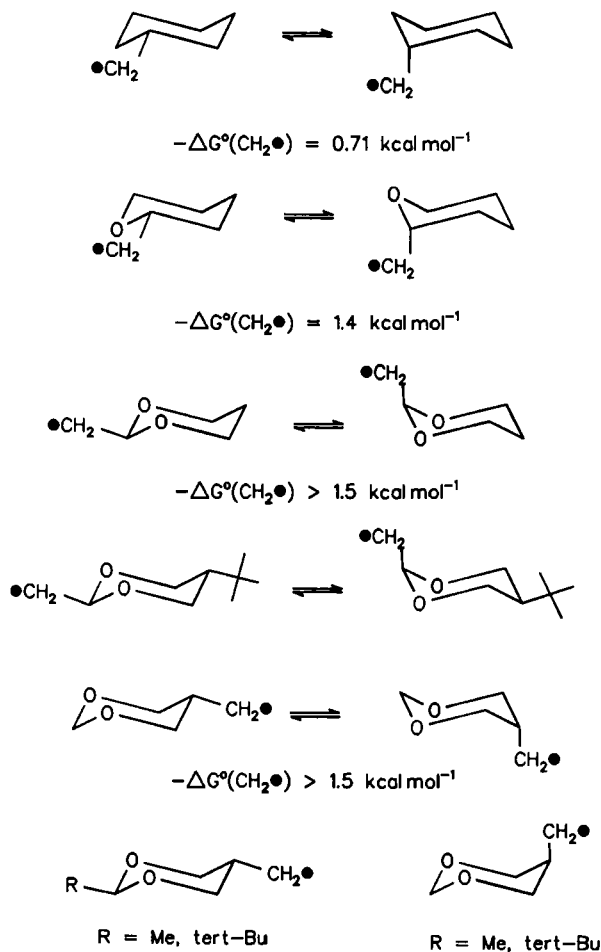
The  $^{13}\text{C}$  chemical shifts of 29 alkyl (Me,Et) substituted oxanes (83OMR94) were used to train a neural network to simulate the  $^{13}\text{C}$  NMR spectra. The neural network, thus trained, was employed to simulate the  $^{13}\text{C}$  NMR spectra of 2-Et, *trans*-3,5-di-Me-, and 2,2,6-tri-Me-oxanes, respectively, compounds that exist >95% in one preferred chair conformation. In one case, the deviation for one methyl substituent proved to be considerable and was related to other conformers participating in the conformational equilibrium (94ACA221).

The EPR spectra of the methyl radicals of oxane and 1,3-dioxane were studied with respect to the conformational energy preference of the  $\text{CH}_2$  group (Scheme 6) [91JCS(P2)1893]. Significantly different hyperfine splittings by the  $\beta$ -hydrogens when the  $\text{CH}_2$  group is axial compared to the equatorial conformer enabled the conformational analysis. Only for the (oxane-2-yl)methyl radical could the  $-\Delta G^\circ$  value ( $1.4 \text{ kcal mol}^{-1}$ ) be determined. Preferred conformers ( $-\Delta G^\circ > 1.5 \text{ kcal mol}^{-1}$ ; Scheme 6) were found for the oxane and the 1,3-dioxane methyl radicals. The conformational energy differences of the  $\text{CH}_2$  group in the different ring systems (Scheme 6) were traditionally explained by the presence or absence of steric repulsions between the  $\text{CH}_2$  group and the *syn*-axial hydrogen atoms [91JCS(P2)1893].

## B. 1,2-DIOXANES

Few papers discuss the conformations of 1,2-dioxanes.  $^1\text{H}$  NMR spectroscopy (especially vicinal H,H-coupling constants) of solutions [80JCS(P1)204], X-ray structure analysis of the solid state [79TL2687; 82JCS(P2)1523; 89TL461] and *ab initio* quantum chemical calculations (HF/6-31G\* level) [91JST(235)25] prove the 1,2-dioxane ring adopts the chair conformation. The same result was obtained in the gas phase by examining the photoelectron spectrum (79LA1473). Hydroxy and methoxy substituents in the 2-position adopt the axial position because of anomeric interactions (89TL461); less polar substituents [alkyl,  $\text{CH}_2\text{Br}$ ,  $\text{CH}_2\text{OH}$ ,  $\text{CH}(\text{Me})\text{COOMe}$ ] prefer the equatorial orientation [79TL2687; 82JCS(P2)1523] on the 1,2-dioxane ring.





SCHEME 6

### C. 1,3-DIOXANES AND DERIVATIVES

#### 1. Conformation of the 1,3-Dioxane Ring System

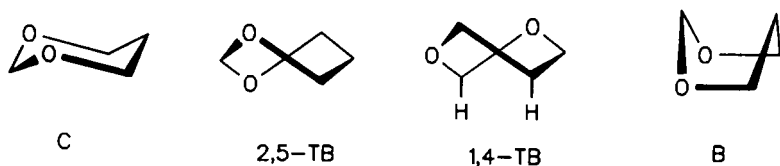
Papers about the conformation of the 1,3-dioxane ring system and the conformational energies of substituents published up to 1976 have been reviewed by Anteunis *et al.* (76H293) and Eliel *et al.* (76JA956). This article covers more recent results and concentrates on some special aspects.

The preferred conformer of 1,3-dioxane is the chair form, as proved by photoelectron spectroscopy (85MI2) and, mainly, by NMR spectroscopy

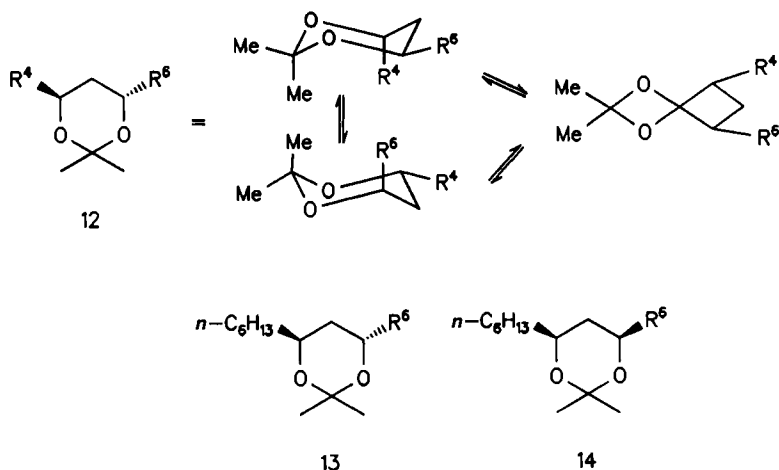
and X-ray structure analysis. However, the boat conformer and two twist conformers (the symmetric 2,5-twist and the unsymmetric 1,4-twist form; Scheme 7) can also participate in the conformational equilibrium. Allinger *et al.* (80IJ51), with the MM1 force field, calculated the twist forms to be 4.81 and 4.93 kcal mol<sup>-1</sup>, respectively, less stable than the chair conformer; the boat conformer was found ca. 1 kcal mol<sup>-1</sup> above the twist forms (corroborated by quantum-chemical *ab initio* calculations at the 6-31G\* level) (88BCJ1619).

Most 1,3-dioxanes adopt chair conformations, but some, because of severe steric interactions (especially 1,3-diaxial), exist in twist-boat conformations. The presence of nonchair conformers can be detected by <sup>1</sup>H NMR spectroscopy; the sum of the coupling constants  $J_{4,5}$  is ca. 11 Hz in the chair conformer but ca. 15 Hz in the twist forms (67BSB157). Based on this criterion, **12** adopts a 2,5-twist-boat conformation (Scheme 8) [68JA3444; 72JCS(P2)252; 74T515]. The enthalpy difference between the twist-boat and the chair conformer of **12** ( $R^4, R^6 = \text{CH}_3$ ) has been estimated to be 7.1 kcal mol<sup>-1</sup> from its heat of combustion (68ACSA2401). Pihlaja *et al.* (80IJ160; 82JOC4688) concluded that compounds **12** ( $R^4, R^6 = \text{CH}_3$ ) exist in a 2,5-twist-boat conformation based on the <sup>13</sup>C chemical shifts. The X-ray data for *trans*-4,6-dialkyl-2,2-dimethyl-1,3-dioxanes corroborated the latter result (84JOC559; 85JOC2095; 90HCA185).

A number of *cis/trans* 4,6-dialkyl-2,2-dimethyl-1,3-dioxanes were studied by <sup>13</sup>C NMR spectroscopy (93JOC5251). The <sup>13</sup>C NMR shifts of C<sup>2</sup>-Me groups (Scheme 8) were found to be very sensitive to the 1,3-dioxane conformation: [chair form: Me(ax) ca. 19 ppm and Me(eq) ca. 30 ppm—pure 30.89 ppm; in the twist-boat form both methyl carbons resonate at ca. 25 ppm (pure 24.70 ppm)]. With these values,  $\Delta G^\circ$  of the chair to twist-boat equilibrium was calculated (Table IV). For **13a** (nitrile), **13b** (alkyne), and **13e** (methyl ester) (Scheme 8) in CH<sub>2</sub>Cl<sub>2</sub>, the temperature dependence of the  $\Delta G^\circ$  values was determined. Depending on the substituent, small negative or positive entropy terms were found; generally the enthalpy term dominates the  $-\Delta G^\circ$  value. In the *trans* isomers **13**, the cyano and alkyne substituents favor the chair conformation, but CHO, ester, alkene, and alkyl substituents, respectively, clearly favor the twist-boat conforma-



SCHEME 7



SCHEME 8

tion (93JOC5251); the  $\text{CF}_3$  group favors the twist-boat conformation by  $> 1 \text{ kcal mol}^{-1}$  (96JOC3662). The *cis* isomers **14** (Scheme 8) prefer the chair form with 4,6-diequatorial substitution. MM3 and PM1 theoretical methods only poorly predict this conformational behavior; semiempirical AM1 and 6-31G *ab initio* quantum-chemical calculations are better, but  $\Delta H^\circ$  values are still poor. 6-31G\* *ab initio* quantum-chemical calculations give reasonable  $\Delta H^\circ$  values (93JOC5251). However, when the relative conformational energies are calculated at the highest level of theory (MP2/6-31G\*), they are well reproduced (95JCC243).

TABLE IV  
CONFORMATIONAL EQUILIBRIA ( $-\Delta G^\circ/\text{kcal mol}^{-1}$ ,  $-\Delta H^\circ/\text{kcal mol}^{-1}$ ,  $-\Delta S^\circ/\text{e.u.}$ ) OF *trans*-2,2,4,6-TETRASUBSTITUTED 1,3-DIOXANES (93JOC5251)

No.	R <sup>6</sup>	Solvent	$-\Delta G^\circ$	$-\Delta H^\circ$	$-\Delta S^\circ$
<b>13a</b>	$\text{C}\equiv\text{N}$	$\text{CDCl}_3$	-0.85		
		$\text{CD}_2\text{Cl}_2$		-0.76	0.47
<b>13b</b>	$\text{C}\equiv\text{CH}$	$\text{CDCl}_3$	-0.26		
<b>13c</b>	$\text{C}\equiv\text{C-}n\text{Bu}$	$\text{CDCl}_3$	-0.12		
		$\text{CD}_2\text{Cl}_2$		-0.15	0.48
<b>13d</b>	$\text{CHO}$	$\text{CDCl}_3$	0.42		
<b>13e</b>	$\text{COOMe}$	$\text{CDCl}_3$	0.77		
		$\text{CD}_2\text{Cl}_2$		0.35	-0.93
<b>13f</b>	$\text{CH}=\text{CH}_2$	$\text{CDCl}_3$	1.20		
<b>13g</b>	$\text{Me}$	$\text{CDCl}_3$	1.76		

Also, 2,2,3,6-tetra-Me-5-Cl-1,3-dioxan, due to 1,3-diaxial interactions, prefers the 2,5-twist-boat form (76BSF563); the same conformation was reported for the stereoisomeric 2-Ph-4-(2'-furyl)-5-NO<sub>2</sub>-6-Me-1,3-dioxanes and 2,2,6-tri-Me-4-(2'-furyl)-5-NO<sub>2</sub>-1,3-dioxanes (75MI2), for 2-Alk-2,4,4-tri-Me-1,3-dioxane derivatives (78KGS1172) and for the *cis* isomers of 2-OR-4-Me-1,3-dioxane (R = Et, *n*Pr, *i*Pr, *n*Bu, *n*-C<sub>8</sub>H<sub>17</sub>) (81DOK116). The corresponding *trans* isomers adopt the chair conformation with di-*eq* substitution. The isomeric 2-OR-4,4-di-Me-1,3-dioxanes also prefer the 1,4-twisted-boat conformer (81DOK116).

The presence of twist-boat forms in the conformational equilibria of 1,3-dioxane derivatives due to the presence of 1,3-diaxial interactions was corroborated by force field calculations [77T2237; 79T691, 79T1945].

## 2. Conformational Energies of Substituents on the 1,3-Dioxane Ring

In addition to the data of Anteunis *et al.* (76H293) and Eliel *et al.* (76JA956), the conformational energies ( $-\Delta G^\circ$ ) of some new substituents were reported (cf. Table V). For several 1,3-dioxane derivatives only the preferred conformations in solution are given. These conformers (together with the solvent employed) are given in Table VI. The  $-\Delta G^\circ$  values of substituents in the 2-position were discussed in terms of steric, polar, and especially stereoelectronic interactions of the substituents and ring oxygen atoms. The last, known as the *anomeric effect*, has been the topic of many reviews and books and is not covered here.

TABLE V  
CONFORMATIONAL ENERGIES (FREE ENERGY DIFFERENCES,  $\Delta G^\circ/\text{kcal mol}^{-1}$ ) OF  
SUBSTITUTED 1,3-DIOXANES

Substituent	Solvent	$-\Delta G^\circ$	Ref.
2-D	Cyclohexand- <i>d</i> <sub>1</sub>	0.05	86JA2109
2-COOEt	CCl <sub>4</sub>	0.92	89T6987
2-SMe	ether	1.73	72JA8587; 76JA956
2-S(O)Me	CDCl <sub>3</sub>	-0.82	72JA8587; 76JA956
2-S- <i>t</i> Bu	CDCl <sub>3</sub>	1.90	87JOC3806; 90JOC33; 92JA2157
2-S(O)- <i>t</i> Bu	CDCl <sub>3</sub>	-0.10	87JOC3806; 90JOC33; 92JA2157
2-SO <sub>2</sub> Me	CDCl <sub>3</sub>	-1.19	72JA8587; 76JA956
2-SO <sub>2</sub> - <i>t</i> Bu	CDCl <sub>3</sub>	1.14	87JOC3806; 90JOC33; 92JA2157
2-S-Ph	CDCl <sub>3</sub>	1.93	87JOC3806; 90JOC33; 92JA2157
2-S(O)-Ph	CDCl <sub>3</sub>	-1.59	87JOC3806; 90JOC33; 92JA2157
2-SO <sub>2</sub> -Ph	CDCl <sub>3</sub>	0.44	87JOC3806; 90JOC33; 92JA2157
2-S(O)-cHex	CDCl <sub>3</sub>	-0.81	87JOC3806; 90JOC33; 92JA2157
2-SO <sub>2</sub> -cHex	CDCl <sub>3</sub>	0.0	87JOC3806; 90JOC33; 92JA2157

TABLE VI  
PREFERRED CHAIR CONFORMERS OF SUBSTITUTED 1,3-DIOXANES IN SOLUTION

Solvent	R <sup>2</sup>	R <sup>4</sup>	R <sup>5</sup>	R <sup>6</sup>	Ref.
CDCl <sub>3</sub>	<i>eq</i> -2-Me	4,4-di-Me	—	6,6-di-Me	82ZOR406
CCl <sub>4</sub>	<i>eq</i> -2(2'-furyl) <sup>a</sup>	—	5,5-di-Me	—	84ZSK168
CCl <sub>4</sub>	<i>eq</i> -2[2-(5-NO <sub>2</sub> -furyl)]	—	5,5-di-Me	—	84ZSK168
Acetone- <i>d</i> <sub>6</sub>	<i>eq</i> -2-Me	—	<i>ax</i> -5-NO <sub>2</sub> - <i>eq</i> -5-Ph	—	90ZSK121
Acetone- <i>d</i> <sub>6</sub>	<i>eq</i> -2-Ph	—	<i>ax</i> -5-NO <sub>2</sub> - <i>eq</i> -5-Ph	—	90ZSK121
CDCl <sub>3</sub>	<i>eq</i> -2-Ph- <i>X</i> <sup>b</sup>	—	<i>eq</i> - <i>n</i> -Alk <sup>b</sup>	—	92ZOR1296
CDCl <sub>3</sub>	2,2-di-Me	<i>eq</i> -4-(CH <sub>2</sub> ) <sub>3</sub> CH = CH <sub>2</sub>	<i>eq</i> -5-Me	—	93JCR(S)328
CDCl <sub>3</sub>	2,2-di-Me	<i>eq</i> -4-(CH <sub>2</sub> ) <sub>3</sub> CH = CH <sub>2</sub>	<i>ax</i> -5-Me	—	93JCR(S)328
CDCl <sub>3</sub>	<i>eq</i> -2-R <sup>c</sup>	—	5,5-di-COOEt	—	79MI2
CDCl <sub>3</sub>	2,2-di-R <sup>c</sup>	—	5,5-di-COOEt	—	792
CDCl <sub>3</sub>	<i>eq</i> -Ph(subst.)	—	5- <i>ax</i> -NO <sub>2</sub> <sup>d</sup> -5- <i>eq</i> -CH <sub>2</sub> OH	—	89M725
CDCl <sub>3</sub>	<i>eq</i> -Ph(subst.)	—	5- <i>ax</i> -NHOH-5- <i>eq</i> -CH <sub>2</sub> OH	—	89M725
CDCl <sub>3</sub>	<i>eq</i> -Ph(subst.)	—	5- <i>ax</i> -N(O) = CHPh <sup>d</sup> -5- <i>eq</i> -CH <sub>2</sub> OH	—	89M725
CDCl <sub>3</sub>	2- <i>eq</i> -Ph( <i>p</i> -Br) <sup>e</sup>	—	—	—	92MRC1019
CDCl <sub>3</sub>	2- <i>eq</i> - <i>i</i> -Pr <sup>e</sup>	—	—	—	92MRC1019
CDCl <sub>3</sub>	2- <i>eq</i> -Me-2- <i>ax</i> -Ph <sup>e</sup>	—	—	—	92MRC1019
CDCl <sub>3</sub>	2- <i>eq</i> -P(O)Ph <sub>2</sub>	—	5- <i>ax</i> - <i>t</i> Bu	—	92T4209
CDCl <sub>3</sub>	2- <i>eq</i> -P(O)Ph <sub>2</sub>	—	5- <i>eq</i> - <i>t</i> Bu	—	92T4209
CDCl <sub>3</sub>	2- <i>eq</i> -P(O)Ph <sub>2</sub>	4- <i>eq</i> -Me	—	6- <i>eq</i> -Me	92T4209
CDCl <sub>3</sub>	2- <i>ax</i> -P(O)Ph <sub>2</sub>	4- <i>eq</i> -Me	—	6- <i>eq</i> -Me	92T4209
CDCl <sub>3</sub>	2- <i>eq</i> -P(O)Ph <sub>2</sub>	—	—	—	92T4209
CDCl <sub>3</sub>	2- <i>eq</i> -P(O)Ph <sub>2</sub>	—	5,5-di-Me	—	92T4209
					88JOC3609
CDCl <sub>3</sub>	2- <i>eq</i> -P(O)Me <sub>2</sub>	—	—	—	88TL6801
CDCl <sub>3</sub>	2- <i>eq</i> -Ph	—	5- <i>ax</i> -Me,5- <i>eq</i> -COMe	—	91MRC613
CDCl <sub>3</sub>	2- <i>eq</i> -Ph	—	5- <i>ax</i> -COMe,5- <i>eq</i> -Me	—	91MRC613
CDCl <sub>3</sub>	2- <i>eq</i> -Ph	—	5- <i>ax</i> -Me,5- <i>eq</i> -CH(OH)Me	—	91MRC613
CDCl <sub>3</sub>	2- <i>eq</i> -Ph	—	5- <i>ax</i> -CH(OH)Me,5- <i>eq</i> -Me	—	91MRC613
CDCl <sub>3</sub>	2- <i>eq</i> -Ph	—	5- <i>ax</i> -Me,5- <i>eq</i> -COPh	—	91MRC613
CDCl <sub>3</sub>	2- <i>eq</i> -Ph	—	5- <i>ax</i> -COPh,5- <i>eq</i> -Me	—	91MRC613

CDCl <sub>3</sub>	2- <i>eq</i> -Ph	—	5- <i>ax</i> -Me, 5- <i>eq</i> -CH(OH)Ph	—	91MRC613
CDCl <sub>3</sub>	2- <i>eq</i> -Ph	—	5- <i>ax</i> -CH(OH)Ph, 5- <i>eq</i> -Me	—	91MRC613
CDCl <sub>3</sub>	2- <i>eq</i> -Ph	—	5- <i>ax</i> -Me, 5- <i>eq</i> -CH(NH <sub>2</sub> )Ph	—	91MRC613
CDCl <sub>3</sub>	2- <i>eq</i> -Ph	—	5- <i>ax</i> -CH(NH <sub>2</sub> )Ph, 5- <i>eq</i> -Me	—	91MRC613
CCl <sub>4</sub>	2,2-di-CH <sub>2</sub> X <sup>f</sup>	—	—	—	78IZV2441
DMSO- <i>d</i> <sub>6</sub>	2- <i>eq</i> -Me	4- <i>eq</i> -Me	5- <i>eq</i> -OH	—	75BSF1228
CCl <sub>4</sub>	—	4- <i>eq</i> -CH <sub>2</sub> -CH <sub>2</sub> SiMe <sub>3</sub>	5,5-di-Me	—	86KGS1031
CCl <sub>4</sub>	2- <i>eq</i> -CH <sub>2</sub> -CH <sub>2</sub> SiMe <sub>3</sub>	—	5,5-di-Me	—	86KGS1031
CCl <sub>4</sub>	2,2-spiro-tetrahydrofuran <sup>g</sup>	—	—	—	84KGS162
CCl <sub>4</sub>	2- <i>eq</i> -R <sup>h</sup>	4,4-di-Me	—	—	78ZOR2483
Mixture	—	—	5,5-di-Cl	—	77ZOR1103
Mixture	2- <i>eq</i> -Me	—	5,5-di-Cl	—	77ZOR1103
Mixture	2- <i>eq</i> -Me	—	5- <i>ax</i> -Cl	—	77ZOR1103
Mixture	2- <i>eq</i> -Me	—	5- <i>eq</i> -Cl	—	77ZOR1103
CS <sub>2</sub>	2- <i>eq</i> -Me	—	5- <i>ax</i> -Cl	—	75BSF2077
CS <sub>2</sub>	2- <i>eq</i> -Me	—	5- <i>eq</i> -Cl	—	75BSF2077
CS <sub>2</sub>	—	4- <i>eq</i> -Me	5- <i>ax</i> -Cl	6- <i>eq</i> -Me	75BSF2077
CS <sub>2</sub>	2- <i>eq</i> -Me	4- <i>eq</i> -Me	5- <i>ax</i> -Cl	6- <i>eq</i> -Me	75BSF2077
CS <sub>2</sub>	2- <i>eq</i> -Me	4- <i>eq</i> -Me	5- <i>eq</i> -Cl	6- <i>eq</i> -Me	75BSF2077
CS <sub>2</sub>	2- <i>eq</i> -Me	4- <i>eq</i> -Me	5- <i>ax</i> -Cl	6- <i>ax</i> -Me	75BSF2077
CS <sub>2</sub>	2- <i>eq</i> -Me	4- <i>eq</i> -Me	5- <i>eq</i> -Cl	6- <i>eq</i> -Me	75BSF2077
CS <sub>2</sub>	2- <i>eq</i> -Me	—	5,5-di-Cl	—	75BSF2077
CS <sub>2</sub>	2- <i>eq</i> -Me	4- <i>eq</i> -Me	5,5-di-Cl	6- <i>eq</i> -Me	75BSF2077
CS <sub>2</sub>	2- <i>eq</i> -Me	4- <i>eq</i> -Me	5,5-di-Cl	6- <i>ax</i> -Me	75BSF2077
CDCl <sub>3</sub>	2,2-di-Me	—	5- <i>eq</i> -CH <sub>2</sub> CH = CH <sub>2</sub>	—	89JCS(CC)954

<sup>a</sup> Furan ring coinciding with the plane of symmetry of 1,3-dioxane ring.

<sup>b</sup> X = -COO-Cyclohexyl-(4-*n*Bu); Alk = *n*-Alkyl, C<sub>3</sub>-C<sub>7</sub>, C<sub>9</sub>.

<sup>c</sup> R = *i*Pr, Cyclohexyl, Phenyl, -C<sub>6</sub>H<sub>4</sub>-*p*-NO<sub>2</sub>; R' = di-Me, -CH<sub>2</sub>(CH<sub>2</sub>)<sub>*n*</sub>CH<sub>2</sub> (*n* = 1-3).

<sup>d</sup> Conformation of 5-axial substituent: *ax* ⊥ (Θ ca. 90°).

<sup>e</sup> By application of a LIS study.

<sup>f</sup> X = Cl, Br; the axial substituent had the halogen directed toward the ring.

<sup>g</sup> The THF oxygen in equatorial conformation; several 2- and 2,2-disubstituted derivatives also studied (all in the given anancomeric conformation).

<sup>h</sup> R = H, Me, Et, *n*Pr, *i*Pr, *n*Bu, *i*Bu, C<sub>5</sub>H<sub>11</sub>, C<sub>6</sub>H<sub>13</sub>, C<sub>8</sub>H<sub>17</sub>.

Deuterium, because of  $n \rightarrow \sigma^*$  hyperconjugation, slightly prefers the equatorial position (86JA2109). The polar COOEt substituent in position 2 of 1,3-dioxane was found also predominantly in an equatorial orientation (see Table V). However, taking the different steric conditions of 1,3-dioxane with respect to cyclohexane into account, a strong anomeric effect of  $-1.91 \text{ kcal mol}^{-1}$  was still observed (89T6987). Hence, the preferred equatorial position of the  $\text{NMe}_2$  group (84KGS756) and the  $\text{P(O)Ph}_2$  substituent in position 2 can be appreciated. The  $\text{P(O)Ph}_2$  substituent (due to destabilizing 1,3-diaxial interactions) so strongly prefers the equatorial conformation in position 2 of 1,3-dioxane [corroborated by force-field calculations (89JOC2859)] that the equilibrium of *cis*-2- $\text{P(O)Ph}_2$ -5-Alk-1,3-dioxane yields  $>95\%$  2-*eq*- $\text{P(O)Ph}_2$ -5-*ax*-Me-1,3-dioxane (89JPO349) and even  $>95\%$  2-*eq*- $\text{P(O)}_2\text{Ph}$ -5-*ax*-*t*Bu-1,3-dioxane (89JOC5191).

In some 2-alkoxy-substituted 1,3-dioxanes (OR: R = Me, Et, *n*Pr, *i*Pr, *t*Bu) and the 2,4,5,5-tetramethyl derivatives, the alkoxy substituent proved to be in the axial position (81KGS1182). Similarly, the  $\text{CH}_2\text{OH}$  group in position 2 is also favored in the axial conformation in a number of 2-Et-2- $\text{CH}_2\text{OH}$ -5-R-5-R<sup>1</sup>-1,3-dioxanes (R = R<sup>1</sup> = H; R = R<sup>1</sup> = Me; R = Me, R<sup>1</sup> = Et; R = R<sup>1</sup> = Et; R = Me, R<sup>1</sup> = *n*Pr; R = Me, R<sup>1</sup> = *i*Bu); the corresponding conformers/isomers were qualitatively detected in large excess. Intramolecular H-bonding to one of the ring oxygen atoms, however, could not be detected (82MI2, 82MI3).

The conformational energies of the 2-Me, 2-OH, 2-OMe, and 2-NH<sub>2</sub> substituents on the 1,3-dioxane ring, calculated on the 6-31G\* *ab initio* level [ $-\Delta G^\circ = 4.8 \text{ kcal mol}^{-1}$  (2-Me), 0.5 (2-OH),  $-1.0$  (2-OMe),  $-0.7$  (2-NH<sub>2</sub>)], were found in good agreement with the experiment (94JOC2138); the conformational behavior was discussed in the light of the *exo/endo*-anomeric effect.

Eliel *et al.* (72JA8587; 76JA956) and Juaristi *et al.* (87JOC3806; 90JOC33; 92JA2157) studied the conformational behavior of 5-sulfur-substituted 1,3-dioxanes (see Table V) and discussed the results in terms of the rotamer population of the axial conformer in which steric, electrostatic, and stereoelectronic effects are dominant. The sulfoxides place both the sulfinyl oxygen and the substituent outside the 1,3-dioxane ring; in the sulfone, the position of the *t*Bu substituent is similarly corroborated by an X-ray structure in the solid state.

Eliel *et al.* equilibrated the diastereotopic 2-*i*Pr-5-R-1,3-dioxanes, determined their conformational preferences (Table VII) (77JOC1533), and discussed the results in terms of solvent effects and various repulsive and attractive interactions between the 5-substituent and the ring oxygen atoms (as visualized in Scheme 9).

The configurational equilibrium of *cis/trans*-2-*i*Pr-5-I-1,3-dioxane heavily favors the *trans* isomer (in 2-*eq*-5-*eq* conformation;  $-\Delta G^\circ = 1.92 \text{ kcal mol}^{-1}$

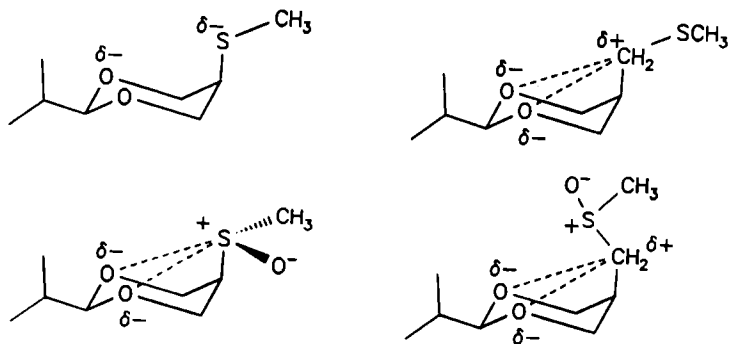
TABLE VII  
POSITION OF CONFIGURATIONAL EQUILIBRIA OF  
2-*i*Pr-5-R-SUBSTITUTED 1,3-DIOXANES IN  
CYCLOHEXANE (77JOC1533)

Subst. R	Temp.	$-\Delta G^\circ$ kcal mol <sup>-1</sup>
SMe	26.5	1.82
CH <sub>2</sub> SMe	41	0.05
(CH <sub>2</sub> ) <sub>2</sub> SMe	41	0.40
OMe	25	1.03
CH <sub>2</sub> OMe	41	-0.05
(CH <sub>2</sub> ) <sub>2</sub> OMe	41	0.53
SOMe	54	-0.6
CH <sub>2</sub> SOMe	50 <sup>a</sup>	-0.14
(CH <sub>2</sub> ) <sub>2</sub> SOMe	50 <sup>a</sup>	0.40
SO <sub>2</sub> Me	50	-1.16
CH <sub>2</sub> SO <sub>2</sub> Me	50 <sup>a</sup>	-0.30
(CH <sub>2</sub> ) <sub>2</sub> SO <sub>2</sub> Me	50 <sup>a</sup>	0.12
S <sup>+</sup> Me <sub>2</sub> Ts <sup>-</sup>	25 <sup>b</sup>	-2.0
S <sup>+</sup> Me <sub>2</sub> PF <sub>6</sub> <sup>-</sup>	25 <sup>b</sup>	-0.63

<sup>a</sup> In benzene.

<sup>b</sup> In CD<sub>3</sub>CN.

in cyclohexane) [77JCS(CC)911]; the more polar the solvent, the more the *cis* isomer (in 2-ax-5-*eq* conformation) participates in the configurational equilibrium. The conformational equilibrium of *trans*-2-C<sub>6</sub>H<sub>4</sub>(*p*CN)-5-XCH<sub>2</sub>CH<sub>3</sub>-1,3-dioxane in nonpolar solvents is also largely shifted to the di-*eq* conformer [ $-\Delta G^\circ$  = 4.23 (*n*-Pr), 5.96 (OEt), 7.64 kcal mol<sup>-1</sup> (SEt)] (88T1609); the liquid-crystalline behavior of such compounds could be derived from this information.



SCHEME 9

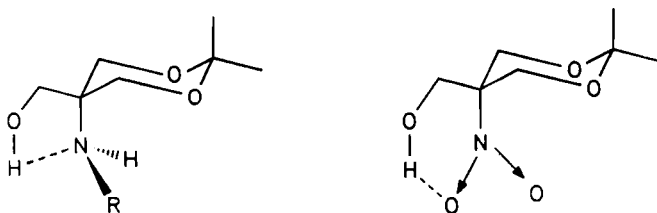


In *r*-4-Me,*cis*-5-Cl,*trans*-6-Me-1,3-dioxane, the chloro substituent prefers the equatorial position ( $-\Delta G^\circ = 1.0 \text{ kcal mol}^{-1}$ ), as in the monosubstituted analog (76BSF563). The pyrimidine ring in position 5 of 2,2-di-*i*Pr-5-(2'-uracilyl)-1,3-dioxane, in the *cis/trans* isomeric 2-EtO-5-(2-uracilyl)-1,3-dioxanes and in 2-Me-2-EtO-5-(2'-uracilyl)-1,3-dioxanes, proved to be in the axial position, assigned by both  $^1\text{H}$  NMR spectroscopy [employing  $\text{Eu}(\text{fod})_3$  as a shift reagent] and X-ray structure analysis (81KGS1523).

By equilibrating ( $\text{BF}_3$ ) the *cis/trans* isomers of 2-Ph-5-OR-1,3-dioxanes, the conformational free energy differences were determined [ $-\Delta G^\circ = 0.24 \text{ kcal mol}^{-1}$  (OMe),  $0.01$  (OTs),  $-0.34$  ( $\text{OSO}_2\text{C}_6\text{H}_4-p\text{NO}_2$ ),  $-0.48$  ( $\text{OSO}_2\text{CH}_3$ )] and discussed with respect to the steric and the attractive *gauche* O—C—C—O effect (92T5941).

In the conformational equilibria of 2,2-di-Me-5-R-5-R<sup>1</sup>-1,3-dioxanes (R = Me,  $\text{CH}_2\text{OH}$ ,  $\text{CH}_2\text{OAc}$ ; R<sup>1</sup> = NHBz,  $\text{NO}_2$ ), both the NHBz and the nitro group prefer the axial position in the chair conformations; in the case of R =  $\text{CH}_2\text{OH}$ , intramolecular hydrogen bonding proved to further stabilize this conformational behavior (Scheme 10) (85KGS468).

In the 5-positions of the 1,3-dioxane ring, the acetyl group usually prefers the equatorial orientation ( $-\Delta G^\circ = 0.40 \text{ kcal mol}^{-1}$  in acetone- $d_6$ ), but in 5-COMe-5-Alk-1,3-dioxanes it is predominantly in the axial position [Alk = *n*Bu:  $-\Delta G^\circ = -0.72 \text{ kcal mol}^{-1}$  (in  $\text{CS}_2$ ); Alk = Et:  $-\Delta G^\circ = -0.88 \text{ kcal mol}^{-1}$  (in acetone- $d_6$ ); Alk = Me:  $-\Delta G^\circ = -0.75 \text{ kcal mol}^{-1}$  (in  $\text{CS}_2$ ) (82CJC1962). The same situation was found in 5-R-5-Me substituted 1,3-dioxanes at low temperature by  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy; the polar substituents R prefer the axial position [R = COMe ( $-\Delta G^\circ = -0.76 \text{ kcal mol}^{-1}$ ); R =  $\text{CH}(\text{OH})\text{Me}$  ( $-\Delta G^\circ = -0.26 \text{ kcal mol}^{-1}$ ), R = CPh ( $-\Delta G^\circ = -0.72 \text{ kcal mol}^{-1}$ ); R =  $\text{CH}(\text{OH})\text{Ph}$  ( $-\Delta G^\circ = -1.07 \text{ kcal mol}^{-1}$ )] (91MRC613; 84CJC1308). The equilibrium of the 5-amino derivative [R =  $\text{CH}(\text{NH}_2)\text{Me}$ ] was not frozen out, but on comparison with the NMR data of anancomeric derivatives, this group shows a marked preference for the axial conformation. The corresponding *cis/trans* isomers of the 2-Ph-5-R-5-Me-dioxanes proved anancomeric (see Table VI).



SCHEME 10

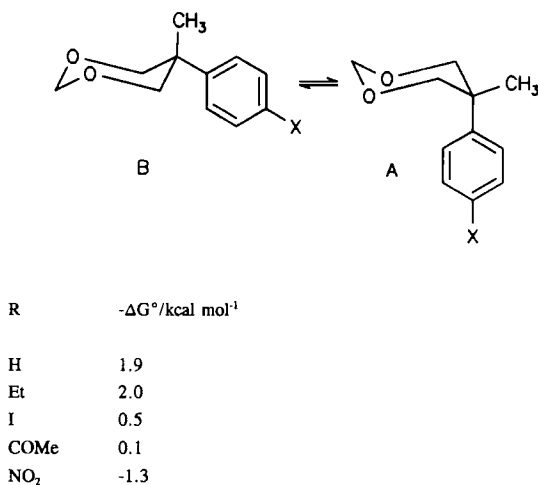
Cook *et al.* (86TL3853) found the conformational equilibrium of 5-Me-5-C<sub>6</sub>H<sub>4</sub>X(*p*)-1,3-dioxane to be strongly dependent on the electron-withdrawing character of the phenyl substituent; more electronegative substituents shift the equilibrium to the 5-*eq*-Me-5-*ax*-C<sub>6</sub>H<sub>4</sub>X(*p*) conformer A (Scheme 11).

The *cis* isomers of 2-Me-4-R-4-OPh-1,3-dioxanes (R = H, Me, Et, *n*Pr, *i*Pr) adopt chair conformations with an axial OPh group (75KGS1936); the *trans* isomers have the OPh substituent predominantly in an equatorial position.

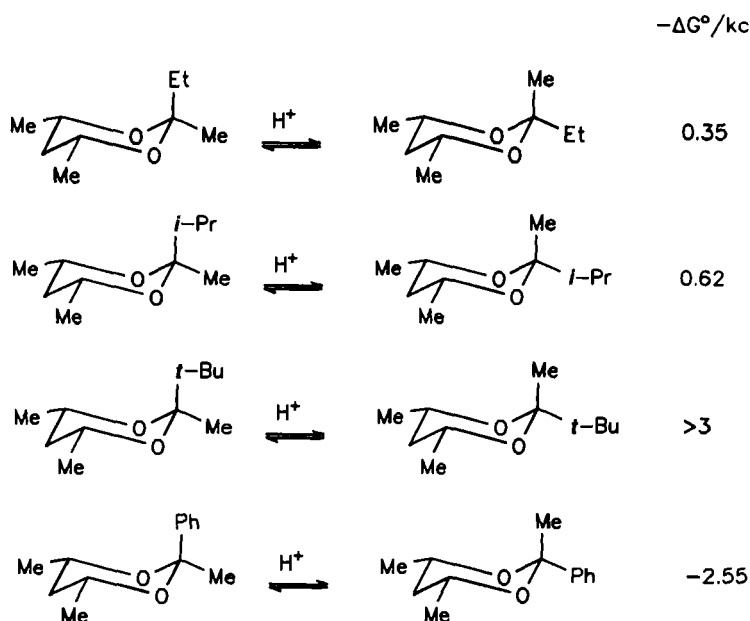
Bailey and Rivera (87JOC1559) studied the effect of MgBr<sub>2</sub> complexation on the equilibrium (2-*ax*-OMe-5-*eq*-Me  $\rightleftharpoons$  2-*eq*-OMe-5-*eq*-Me:  $-\Delta G^\circ = -0.36$  kcal mol<sup>-1</sup> in favor of the 2-*ax*-5-*eq* conformer) and found a dramatic effect (2-*ax*-OMe MgBr<sub>2</sub>-5-*eq*-Me  $\rightleftharpoons$  2-*eq*-OMe MgBr<sub>2</sub>-5-*eq*-Me:  $-\Delta G^\circ = 1.36$  kcal mol<sup>-1</sup> in favor of the 2-*eq*-5-*eq* conformer).

The equilibria of the *cis/trans* isomers of 2-Me,*r*-2-Ph,*cis*-5-Ph-1,3-dioxane are in favor of the 2-*eq*-Me-2-*ax*-Ph-5-*eq*-Ph-1,3-dioxane conformer ( $-\Delta G^\circ = -1.05$  kcal mol<sup>-1</sup>) (85JOC4439).

The equilibria of the diastereomers of 2-Alk-2,4,6-tri-Me-1,3-dioxanes and 2-Ph-2,4,6-tri-Me-1,3-dioxanes were studied by equilibration (in ether at 25°C (78JA2202) (Scheme 12); the more bulky 2-Alk substituent goes into the equatorial position in line with well-known conformational principles [78ACSA(B)769; 95H2233]. The configuration and conformation of a multitude of 5-alkyl-, 5,5-dialkyl-, 2,2-di-Me-5-alkyl-, and 2,2,4,5-tetra-Me-5-alkyl-1,3-dioxanes were studied by <sup>1</sup>H NMR spectroscopy (75T489); the



SCHEME 11



SCHEME 12

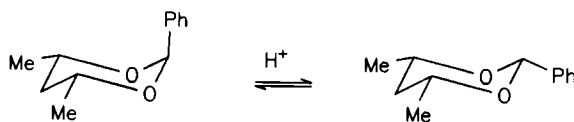
more voluminous 5-substituent (in the *cis* isomers) tends toward the axial position as expected. Also, GC retention times were found to be dependent on conformational differences in 2,5,5-tri-alkyl-1,3-dioxanes (79MI4).

Bogatskii *et al.* (71KGS582) studied the equilibria of the diastereotopic 2,5-di-alkyl- and 2,5,5-tri-alkyl-1,3-dioxanes and found that the *trans* isomers were more stable by 0.74–0.98 kcal mol<sup>-1</sup> (di-*eq* conformation is favored; otherwise, the more bulky substituent in position 5 goes into the axial position) (86ZOR217; 88ZOR1106).

### 3. Conformational Behavior of 2-Phenyl Substituents on the 1,3-Dioxane Ring

Bailey *et al.* (76LA2240; 78JA2202) reported the calorimetric heat of acid-catalyzed isomerization of diastereomeric *r*-2-phenyl,*cis*-4-Me,*cis*-6-di-Me-1,3-dioxanes (Scheme 13). The conformational free energy of phenyl at C-2 ( $-\Delta G^\circ = 3.12$  kcal mol<sup>-1</sup>) is the result of a  $-\Delta H^\circ = 2.01$  kcal mol<sup>-1</sup> favoring the equatorial orientation and a large conformational entropy  $-\Delta S^\circ = -3.9$  cal K<sup>-1</sup> mol<sup>-1</sup> also favoring the equatorial conformer.

With respect to the principal axis of symmetry of the 1,3-dioxane ring, the 2-phenyl substituent can adopt four characteristic rotamers (Scheme 14) (90MI2).



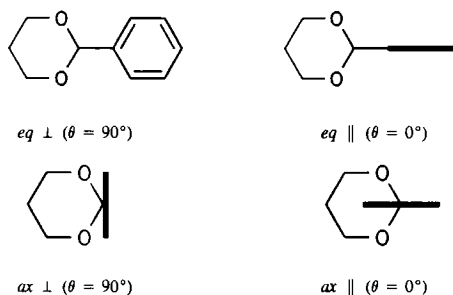
SCHEME 13

Bailey *et al.* (76LA2240; 78JA2202) found axial 2-phenyl in the perpendicular conformation  $ax \perp$  ( $\Theta = 90^\circ$ —corroborated by X-ray analysis (75TL1207) because of the absence of significant *ortho*-hydrogen compressions (as concluded also from the low  $-\Delta H^\circ$  value of the isomerization)). The axial phenyl substituent oscillates about an average of the perpendicular conformation; the barrier to rotation proved sizable. In the 2-*eq*-position, the phenyl ring rotates more or less freely [ $\Delta G^\ddagger = 2.0$  kcal mol $^{-1}$  (79CJC355)] as suggested by the large  $-\Delta S^\circ$  value, which indicates a substantial difference between the freedom of internal rotation about C-2 to phenyl in the two diastereomers. The preferred conformations for 2-*eq*-Ph-1,3-dioxanes reported for the solid state are dependent primarily on packing forces.

In 2-Me-2-Ph-substituted 1,3-dioxanes, the phenyl substituent proved to adopt the  $ax \perp$  ( $\Theta = 90^\circ$ ) conformation in the solid state (87ZSK124). Other preferred rotamers of 2-Ph-substituted 1,3-dioxanes in the solid state have been reported (Table VIII).

#### 4. Conformation of 1,3-Dioxanes in the Solid State

The X-ray crystal structures of a number of differently substituted 1,3-dioxanes have been published; the structures of chair conformers are given in Table IX. The influence of substitution on the geometry of the 1,3-dioxane ring in the solid state has been discussed in detail in two reviews (88ZSK110; 90MI2).



SCHEME 14

TABLE VIII  
PREFERRED CONFORMERS OF 2-PH-SUBSTITUTED 1,3-DIOXANES IN THE SOLID STATE  
(CHAIR CONFORMATION)

Rotamer	R <sup>2</sup>	R <sup>4</sup>	R <sup>5</sup>	R <sup>6</sup>	Ref.
<i>eq</i>    ( $\Theta = 41^\circ$ )	-Ph- <i>p</i> Br	—	<i>n</i> -C <sub>6</sub> H <sub>13</sub>	—	81MI3
<i>eq</i>    ( $\Theta = 48.8^\circ$ )	-Ph	—	Me	—	84MI1
<i>eq</i>    ( $\Theta = 20.8^\circ$ )	-Ph- <i>p</i> Cl	—	5- <i>ax</i> -COMe,5- <i>eq</i> -Me	—	84MI1
<i>eq</i>    ( $\Theta = 49^\circ$ )	-Ph	—	5- <i>ax</i> -OH,5- <i>eq</i> - <i>i</i> Pr	—	77AX925
<i>eq</i>    ( $\Theta = 27.2^\circ$ )	-Ph- <i>p</i> Br	4-Me	—	6-Me	75TL1207
<i>ax</i> ⊥ ( $\Theta = 89.9^\circ$ )	-Ph- <i>p</i> CF <sub>3</sub>	4-Me	—	6-Me	75TL1591
<i>eq</i> ⊥ ( $\Theta = 90^\circ$ ) <sup>a</sup>	-Ph- <i>p</i> X	—	—	—	75IZV1073
<i>ax</i> ⊥ ( $\Theta = 90^\circ$ )	2- <i>eq</i> -Me-2- <i>ax</i> -Ph	—	5- <i>eq</i> -Ph	—	85JOC4439
<i>ax</i>    ( $\Theta = 31^\circ$ )	2- <i>eq</i> -Me-2- <i>ax</i> -Ph	—	5- <i>ax</i> -Ph <sup>b</sup>	—	85JOC4439
<i>ax</i> ⊥ <sup>c</sup>	2- <i>eq</i> -Me-2- <i>ax</i> -Ph	—	—	—	77M113
<i>ax</i>    , <i>eq</i> ⊥ <sup>c</sup>	2- <i>eq</i> -Ph-2- <i>ax</i> -Ph	—	—	—	77M113
<i>eq</i>    , <i>ax</i> ⊥ <sup>c</sup>	2- <i>eq</i> -Ph · Cr(CO) <sub>3</sub> - 2- <i>ax</i> -Ph	—	—	—	77M113
<i>eq</i>    ( $\Theta = 30^\circ$ ) <sup>c</sup>	2- <i>eq</i> -Ph · Cr(CO) <sub>3</sub>	—	—	—	77M113
<i>ax</i> ⊥ ( $\Theta = 90^\circ$ ) <sup>a</sup>	2- <i>ax</i> -Ph	—	—	—	76BSB103
	2- <i>ax</i> -Ph-2- <i>eq</i> -Me	—	—	—	76M1
<i>eq</i> ⊥ (twisted) <sup>a,d</sup>	2- <i>eq</i> -Ph	—	—	—	76BSB103
<i>eq</i> ⊥ ( $\Theta = 90^\circ$ ) <sup>a</sup>	2-Ph- <i>p</i> X	—	—	—	75IZV1070
<i>eq</i> ⊥ ( $\Theta = 90^\circ$ ) <sup>a</sup>	2-Ph- <i>p</i> X	—	5,5-di-Cl	—	75IZV1070

<sup>a</sup> In solution from dipole moments.

<sup>b</sup> Conformation of 5-Ph: *ax* || ( $\Theta = 31^\circ$ ).

<sup>c</sup> In solution from dipole moments and NMR studies.

<sup>d</sup> The influence of *ortho*-, *meta*-, and *para*-phenyl substituents on both the torsional barrier and the preferred rotamer studied in Keller *et al.* (76M949).

## 5. Intramolecular Hydrogen Bonding in 1,3-Dioxane Derivatives

5-Hydroxy-1,3-dioxane both in the gaseous state and in dilute CCl<sub>4</sub> solution exists as a chair conformer, the hydroxy group in an axial position with an intramolecular hydrogen bond of the O—H · · · O type (76TL2065; 80JA1248) (the axial conformer is more stable by  $\Delta G^\circ = 1.2$  kcal mol<sup>-1</sup>) [81AQ(A)76]. Microwave spectroscopy and the <sup>3</sup>J<sub>H(5eq),OH</sub> coupling constant suggest that the OH group lies in the plane of symmetry and is a part of a bifurcated hydrogen bond to the two ring oxygens (Scheme 15) (76TL2065; 80JA1248). The MM2 force field corroborated these experimental findings (80IJ51). The same hydrogen bonding is present in the *cis* isomers of 2-Me-5-R-5-OH-1,3-dioxanes (R = H, Me) **15** in benzene solution as detected by IR spectroscopy (Scheme 15) (75BSF1237). The corre-

TABLE IX  
X-RAY CRYSTAL STRUCTURES OF SUBSTITUTED 1,3-DIOXANES (IN CHAIR CONFORMATION)

R <sup>2</sup>	R <sup>4</sup>	R <sup>5</sup>	R <sup>6</sup>	Ref.
<i>eq</i> -C <sub>6</sub> H <sub>4</sub> - <i>p</i> Br <sup>a</sup>	—	<i>eq</i> - <i>n</i> C <sub>6</sub> H <sub>13</sub> <sup>a</sup>	—	81MI3
2,2-di-Me	—	<i>ax</i> -(2-uracil)	—	81KGS1523
<i>eq</i> -2-Ph <sup>b</sup>	—	<i>ax</i> -5-NO <sub>2</sub> - <i>eq</i> -5-Ph <sup>c</sup>	—	90ZSK121
2- <i>eq</i> -P(O)Ph <sub>2</sub>	4- <i>eq</i> -Me	—	6- <i>eq</i> -Me	92T4209
2- <i>ax</i> -P(O)Ph <sub>2</sub>	4- <i>eq</i> -Me	—	6- <i>eq</i> -Me	92T4209
2- <i>eq</i> - <i>t</i> Bu	—	5- <i>ax</i> -SO <sub>2</sub> - <i>t</i> Bu <sup>d</sup>	—	92JA2157
2- <i>eq</i> - <i>t</i> Bu	—	5- <i>eq</i> -SO <sub>2</sub> - <i>t</i> Bu	—	92JA2157
2- <i>eq</i> - <i>t</i> Bu	—	5- <i>ax</i> -SO- <i>t</i> Bu	—	92JOC5963
2- <i>eq</i> -P(O)Ph <sub>2</sub>	—	5,5-di-Me	—	88JOC3609
2- <i>eq</i> -P(O)Me <sub>2</sub>	—	—	—	88TL6801
2- <i>eq</i> -C(Br)=CHPh <sup>e</sup>	—	4- <i>eq</i> -Me	6- <i>eq</i> -Me	77BAP707
2- <i>eq</i> -C(Br)=CHPh	—	5,5-di-Me	—	77BAP863
2- <i>eq</i> -COPh-	—	—	—	81AX(B)621
<i>p</i> R(R=Me,F,Cl)				
2- <i>eq</i> -C(Br)=CHPh	4-Me	—	6,6-di-Me	80BAP103
2- <i>eq</i> - <i>i</i> Pr	—	5- <i>ax</i> -C(S)-NH <sub>2</sub> <sup>f</sup>	—	79AX(C)206
2- <i>eq</i> -OEt	—	5- <i>ax</i> -1-[4-NH <sub>2</sub> (4-Cl)-purinyl] <sup>g</sup>	—	79KGS976, 79MI1; 82MI1
2- <i>ax</i> -OEt	—	5- <i>ax</i> -1-[4-NH <sub>2</sub> (4-Cl)-purinyl]	—	79KGS976, 79MI1; 82MI1
2- <i>eq</i> -Ph	4- <i>eq</i> -R <sup>h</sup>	5- <i>ax</i> -R <sup>i</sup>	—	84BSB1047
2- <i>eq</i> - <i>i</i> Pr	4- <i>eq</i> -Ph	—	—	78MI1

<sup>a</sup> Conformation corroborated by MM2 force field calculations (90MI1).

<sup>b</sup> Conformation *eq* || ( $\Theta = -11.7^\circ$ ).

<sup>c</sup> Conformation *eq* ⊥ ( $\Theta = -85.1^\circ$ ).

<sup>d</sup> The *t*Bu substituent is directed outside the 1,3-dioxane ring.

<sup>e</sup> Slightly twisted-boat conformer with the 3-substituents in equatorial position.

<sup>f</sup> One NH intramolecularly bonded to one ring oxygen atom.

<sup>g</sup> Rotamer conformation of the purine ring *ax* || ( $\Theta = 15-59^\circ$ ) because of weak intramolecular hydrogen bonding.

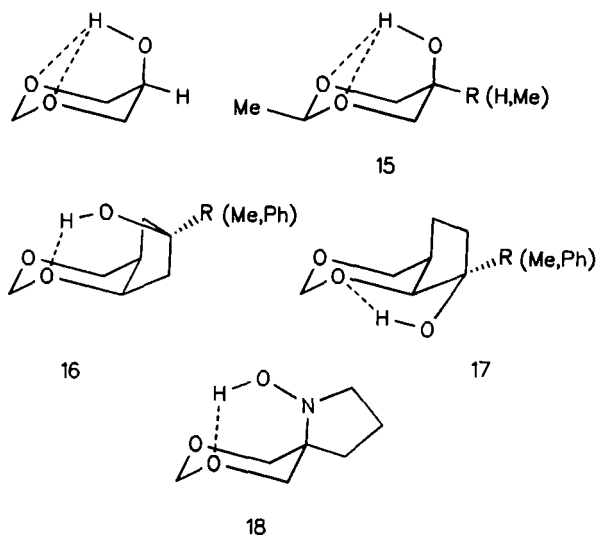
<sup>h</sup> R = Methylene-dioxyphenyl.

<sup>i</sup> R' = -CH(COOMe)-CH(OH)-C<sub>6</sub>H<sub>2</sub>(3,4,5-tri-OMe).

sponding bifurcated H bond could not be found in 5-COOH-1,3-dioxane (92RRC1165).

The axial ⇌ equatorial equilibrium of 5-OH-1,3-dioxane was strongly solvent dependent; alcohols favor the axial position, other solvents, more polar than CCl<sub>4</sub>, the equatorial orientation of the 5-hydroxy substituent, both effects being corroborated by PM3 calculations [92MI3; 93JST(287)185].

Intramolecular hydrogen bonding (due to IR and a detailed NMR study including NOEs) also favors the O-inside conformers of the *cis*-fused cyclo-



SCHEME 15

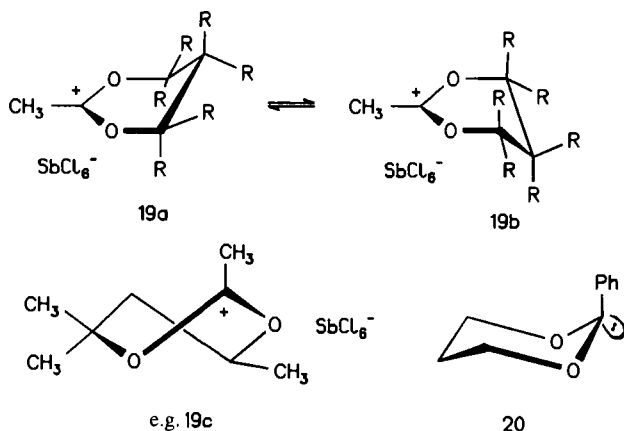
penta[*d*][1,3]dioxanes **16** and **17** (93MRC63) (Scheme 15) and hinders the free N-inversion in the 5-spiro-1,3-dioxane derivative **18** (89M725) (Scheme 15).

#### 6. Conformation of 1,3-Dioxane-2-ylum Ions and the Corresponding Carbanions

A number of 1,3-dioxan-2-ylum ions have been studied with respect to the preferred conformation. From a detailed  $^1\text{H}$  and  $^{13}\text{C}$  NMR study (79OMR616) and the X-ray crystal structural analysis (94CJC2084), it was concluded that the 1,3-dioxan-2-ylum ions adopt the *envelope* conformation with the  $\text{C}^4\text{—O—C}^2\text{—O—C}^6$  moiety in one plane (due to mesomerism) and  $\text{C}^4\text{—C}^5\text{—C}^6$  forming the flap (Scheme 16). Ring interconversion **19a**  $\rightleftharpoons$  **19b** and a 1:1 conformational equilibrium was assumed.

In the case of 2,4,4,6-tetra-alkyl substitution (due to steric hindrance) the corresponding 1,4-twist-boat conformer **19c** was identified by  $^1\text{H}$  NMR spectroscopy (85ZOR96).

Jernigan and Eliel (95JA9638) studied the stereochemistry of the corresponding 2-carbanions: 2-Ph-1,3-dioxanyl carbanion proved to be pyramidal at the 2-position with the lone pair in an equatorial orientation (**20**); the 4-Ph-1,3-dioxanyl carbanion appears to be planar with slow rotation about the  $\text{C}(4)\text{—C}(\textit{ipso})$  partial double bond on the NMR timescale at  $-40^\circ\text{C}$ .



SCHEME 16

### 7. Conformation of 1,3-Dioxan-2-ones, 1,3-Dioxan-4-ones, and Meldrum's Acid Derivatives

Pihlaja and Rossi [83ACSA(B)289] prepared 1,3-dioxan-2-one and all of its methyl derivatives, recorded their  $^{13}\text{C}$  NMR spectra, and derived the methyl substituent shift parameters by a multiple linear regression analysis of the anancomeric and two equivalent chair conformers (Table X). With these values, the authors estimated the conformational equilibria for two unequally populated chair conformations (Nos. 2, 3, 9, 11, and 14 in Table X). A consistent picture of the predominance of the chair conformation and the corresponding chair  $\rightleftharpoons$  chair equilibria in 1,3-dioxan-2-ones was obtained in complete agreement with earlier  $^1\text{H}$  NMR results.

From X-ray structures, two preferred conformers of 1,3-dioxan-4-one derivatives have been reported: the O(1)-sofa conformation (86MI3; 92HCA913] (Scheme 17, **21**, **22**) and the twisted-boat conformation (92HCA913; 94CB565) (Scheme 17, **23**, **24**). Steric hindrance (especially 1,3-diaxial) of substituents strongly controls the populations (76BSF825). The corresponding dioxinones **25**–**27** (Scheme 17) adopt the C(2)-sofa conformation (92HCA913; 96H861) with the electron-withdrawing group in a quasi-axial orientation in accord with the  $n_{\text{O}} \rightarrow \sigma^*_{\text{C}} \rightarrow \sigma^*_{\text{C}}$  interaction (96H861).

The X-ray structures of two 1,3-benzodioxin-4-one derivatives (**28** in Scheme 17) were reported [83T3151; 90AX(C)2416]; the dioxane ring was present in a half-chair conformation with the alkoxy (phenoxy) substituent in an axial orientation.

Äyräs studied the stereochemistry of 2,5-di- and 2,2,5-tri-substituted 1,3-dioxane-4,6-diones (Meldrum's acid derivatives) in  $\text{CCl}_4$  (76MI1, 76MI2).

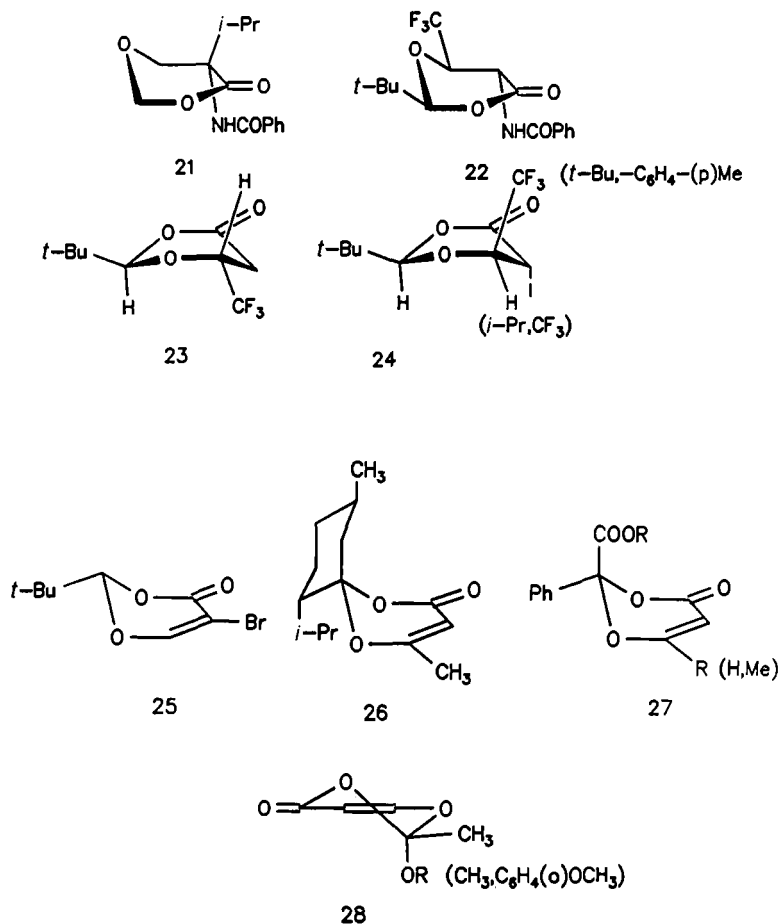


TABLE X  
PREFERRED CONFORMERS AND CONFORMATIONAL EQUILIBRIA OF 1,3-DIOXAN-2-ONES IN  $\text{CDCl}_3$   
AT ROOM TEMPERATURE [83ACSA(B)289]

No.	1,3-Dioxan-2-one	Anancomeric conformations and conformational equilibria	$-\Delta G^\circ$ (kcal mol <sup>-1</sup> )
1	parent	—	—
2	4-Me	4- <i>eq</i> $\rightleftharpoons$ 4- <i>ax</i>	2.29
3	5-Me	5- <i>eq</i> $\rightleftharpoons$ 5- <i>ax</i>	0.68
4	4,4-di-Me	4- <i>eq</i> , 4- <i>ax</i>	—
5	5,5-di-Me	5- <i>eq</i> , 5- <i>ax</i>	—
6	<i>cis</i> -4,6-di-Me	4- <i>eq</i> , 6- <i>eq</i>	—
7	<i>trans</i> -4,6-di-Me	4- <i>eq</i> , 6- <i>ax</i> $\rightleftharpoons$ 4- <i>ax</i> , 6- <i>eq</i>	—
8	<i>trans</i> -4,5-di-Me	4- <i>eq</i> , 6- <i>eq</i>	—
9	<i>cis</i> -4,5-di-Me	4- <i>eq</i> , 5- <i>ax</i> $\rightleftharpoons$ 4- <i>ax</i> , 5- <i>eq</i>	1.74
10	4,4,6-tri-Me	4- <i>eq</i> , 4- <i>ax</i> , 6- <i>eq</i>	—
11	<i>r</i> -4, <i>cis</i> -5, <i>trans</i> -6-tri-Me	4- <i>ax</i> , 5- <i>ax</i> , 6- <i>eq</i> $\rightleftharpoons$ 4- <i>eq</i> , 5- <i>eq</i> , 6- <i>ax</i>	0.42
12	<i>r</i> -4, <i>trans</i> -5, <i>cis</i> -6-tri-Me	4- <i>eq</i> , 5- <i>eq</i> , 6- <i>eq</i>	—
13	<i>r</i> -4, <i>cis</i> -5, <i>cis</i> -6-tri-Me	4- <i>eq</i> , 5- <i>ax</i> , 6- <i>eq</i>	—
14	4,4,5-tri-Me	4- <i>ax</i> , 4- <i>eq</i> , 5- <i>ax</i> $\rightleftharpoons$ 4- <i>eq</i> , 4- <i>ax</i> , 5- <i>eq</i>	1.17
15	4,5,5-tri-Me	4- <i>eq</i> , 5- <i>eq</i> , 5- <i>ax</i>	—
16	4,4,5,5-tetra-Me	4- <i>ax</i> , 4- <i>eq</i> , 5- <i>ax</i> , 5- <i>eq</i>	—
17	4,4,6,6-tetra-Me	4- <i>ax</i> , 4- <i>eq</i> , 6- <i>ax</i> , 6- <i>eq</i>	—
18	<i>cis</i> -4,5,5,6-tetra-Me	4- <i>eq</i> , 5- <i>eq</i> , 5- <i>ax</i> , 6- <i>eq</i>	—
19	<i>trans</i> -4,5,5,6-tetra-Me	4- <i>ax</i> , 5- <i>eq</i> , 5- <i>ax</i> , 6- <i>eq</i> $\rightleftharpoons$ 4- <i>eq</i> , 5- <i>eq</i> , 5- <i>ax</i> , 6- <i>ax</i>	—
20	<i>trans</i> -4,4,5,6-tetra-Me	4- <i>eq</i> , 4- <i>ax</i> , 5- <i>eq</i> , 6- <i>eq</i>	—
21	<i>cis</i> -4,4,5,6-tetra-Me	4- <i>eq</i> , 4- <i>ax</i> , 5- <i>ax</i> , 6- <i>eq</i>	—
22	4,4,5,6,6-penta-Me	4- <i>eq</i> , 4- <i>ax</i> , 5- <i>eq</i> , 6- <i>eq</i> , 6- <i>ax</i>	—
23	4,4,5,5,6-penta-Me	4- <i>eq</i> , 4- <i>ax</i> , 5- <i>eq</i> , 5- <i>ax</i> , 6- <i>eq</i>	—
24	4,4,5,5,6,6-hexa-Me	4- <i>eq</i> , 4- <i>ax</i> , 5- <i>eq</i> , 5- <i>ax</i> , 6- <i>eq</i> , 6- <i>ax</i>	—

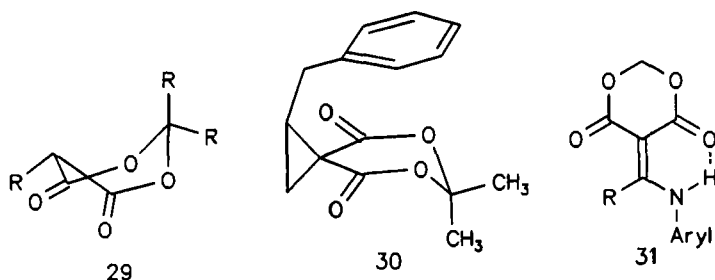
Subject to nonbonded interactions, these compounds adopt the boat conformation **29** (Scheme 18). The phenyl substituents in the 2-position proved to prefer in the axial orientation the perpendicular conformation ( $\Theta = 90^\circ$ ), and in the equatorial position the parallel conformation ( $\Theta = 0^\circ$ ). A 5-substituent was generally found in an equatorial orientation (76M1; 79BSB223). In 2-Et-5,5-di-Me-1,3-dioxan-4,6-dione, the ethyl substituent was present in the equatorial parallel conformation ( $\Theta = 0^\circ$ ) (79BSB223).

In the benzyl-substituted spiro compound **30** (Scheme 18), the phenyl ring (due to a weak intramolecular interaction) was folded over the 1,3-dioxan-3,6-dione moiety (78M1263); the ABMNX spin system in the  $^1\text{H}$  NMR spectrum therefore was analyzed in detail (in  $\text{CDCl}_3$ ).



SCHEME 17

In addition, a few X-ray crystal structures of other substituted Medrum's acid derivatives were reported; planar (2,2-di-Me-5,5-di-CH<sub>2</sub>COOEt-1,3-dioxan-4,6-dione [81JCS(P2)1454]), boat (5,5-di-Me-1,3-dioxan-4,6-dione [77AX(B)3241; 85JCS(P2)1547; 93AX(C)1000]), half boat (5-arylmethylene-1,3-dioxan-4,6-dione [81JCS(P2)1454; 89TL5281], 5-NHMe-methylene-1,3-dioxan-4,6-dione [91AX(C)1028]), and envelope conformers [85AX(C)586] were detected; in the cases of *exo*-methylene-NHR-aryl derivatives, intramolecular hydrogen bonding stabilizes the preferred conformer, as in **31** (Scheme 18).



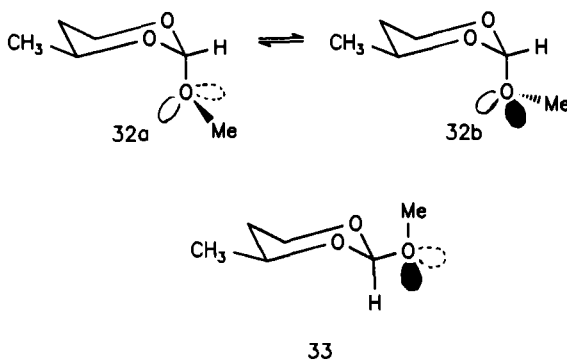
SCHEME 18

### 8. Preferred Rotamers of 2-Methoxy-1,3-dioxanes

In connection with studying the *exo-anomeric effect*, in which the *p*-type orbital of the anomeric oxygen must be oriented *anti* with respect to the C-ring oxygen bond, Rao (82CJC1067) investigated the rotameric conformation of *cis/trans*-2-OMe,4-Me-1,3-dioxane by NOE experiments and the heteronuclear H-2,OCH<sub>3</sub> coupling constant. The *trans* isomer exists in the dynamic equilibrium **32a**  $\rightleftharpoons$  **32b** (Scheme 19) having the *p*-type orbital of the *exo*-cyclic oxygen in an *anti* orientation with respect to the C(2)—O(1) and C(2)—O(3) bonds. In the *cis* isomer, the *exo*-cyclic oxygen was oriented *anti* with respect to the C(2)—O(1) and C(2)—O(3) bonds, respectively, again in a dynamic equilibrium (Scheme 19, averaged conformation **33**).

### 9. Miscellaneous Structures Including the 1,3-Dioxane Ring System

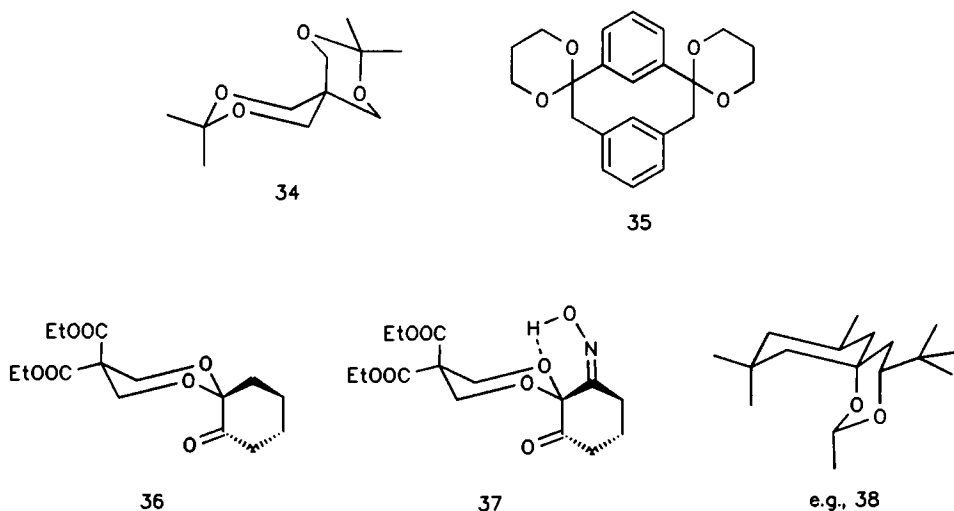
Two major groups of polycyclic compounds including the 1,3-dioxane structure are interesting conformationally. The first, the spiranes, conserve



SCHEME 19

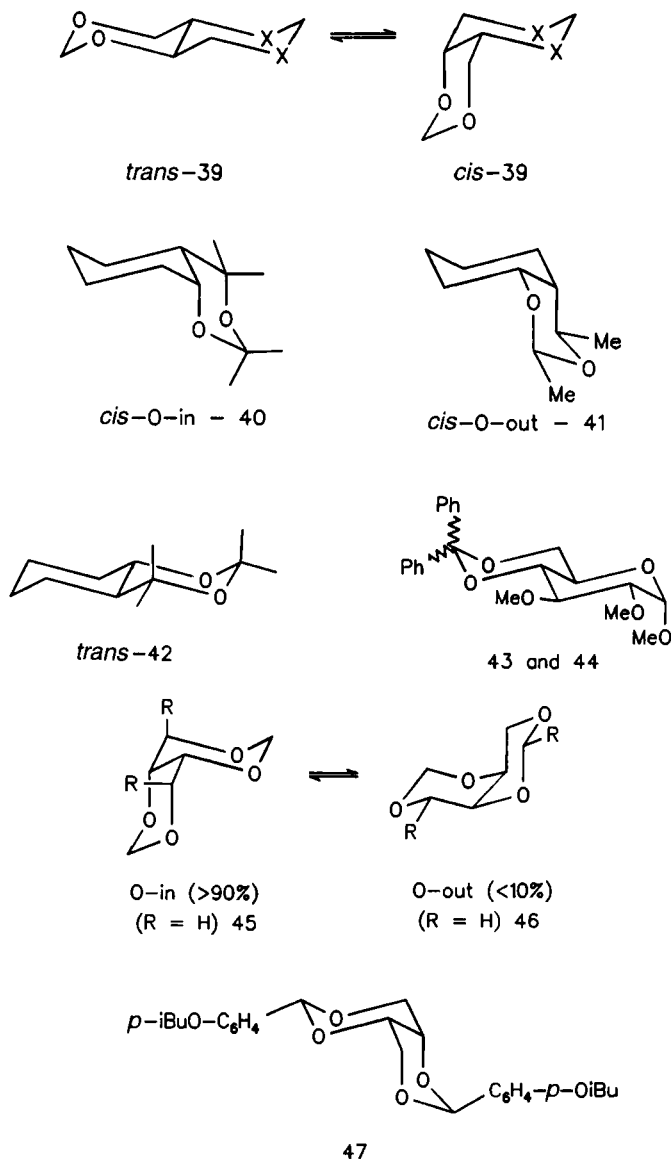
the 1,3-dioxane ring system in chair conformations [for spiro-bis-dioxane derivatives (89M269; 92MI1, 92ZOB649), see **34** in Scheme 20]; at low temperature, the ring interconversion was frozen and chirality/diastereotopism of the spiranes could be studied (92MI1). In case of 2,2'-monosubstitution, the substituents adopt equatorial positions (81ZOB934), and in the case of 2,2'-di-Me,2,2'-di-Ph-tetra-substitution, the methyls adopt equatorial positions and the phenyl rings were found in axial perpendicular ( $\Theta = 90^\circ$ ) conformation (87ZSK124). A similar conformation [ $ax \perp$  ( $\Theta = 75^\circ$ )] was found in the meta-cyclophane **35** (78M719).

The conformational equilibria of 1,3-dioxo-spiro-4-cyclohexane derivatives were assigned by detailed NMR studies (82M565); while the carbonyl carbon in the double chair conformer **36** (Scheme 20) adopts the axial position, the corresponding carbon of the oxime goes into the equatorial orientation (this conformation **37** is stabilized by intramolecular hydrogen bonding) (82M565). In addition, the diastereoisomers of two series of heavily substituted 1,3-dioxane-spiro-4-cyclohexanes (e.g., **38**) have been analyzed (78CJC2998, 78CJC3006) and both the conformational equilibria and the dynamic behavior of some di- and tri-spiro-1,3-dioxanes have been reported [95JCS(P2)1351]. In the case of the dispiro-1,3-dioxanes, a new type of *helical* diastereoisomerism was described and the corresponding isomers assigned by detailed dynamic  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy (96T12783).



SCHEME 20

The second group of compounds are the oxa-decalins, which can exist in *cis*-**39** and *trans*-**39** anellation (Scheme 21). 2,4-Di-substituted 1,3-dioxadecalins exist as a mixture of *cis*- isomers, the oxygen in O-in conformation



SCHEME 21

**40** (only in one case was the O-out conformation **41** found), and *trans* isomers **42** (87T2761). The two epimers of methyl-4,6-*O*-benzylidene-2,3-di-*O*-Me- $\alpha$ -D-glucopyranoside **43, 44** adopt the *trans* double chair conformation with the phenyl substituents in axial and equatorial orientations, respectively [86ACSA(B)119].

The 1,3,5,7-*cis*-tetraoxa-decalin system was studied by NMR spectroscopy and force field calculations. Also in this case, the O-in conformation **45** proved to be preferred over the O-out conformation **46** because of a 1,3-diaxial interaction in the latter conformer (95TA2767). However, the conformational equilibria of the 4,8-di-substituted *cis*-decalin analogs **45**  $\rightleftharpoons$  **46**, because of steric effects of the substituents, are shifted to the O-out conformer [**46** R = Me, 85%; CH<sub>2</sub>OMe, 79%; CH<sub>2</sub>OPiv, 89%; CH<sub>2</sub>O-(CH<sub>2</sub>)<sub>2</sub>OMe, 75%; CH<sub>2</sub>OCH<sub>2</sub>Ph, 75%; CH<sub>2</sub>N<sub>3</sub>, 97%]. The solvent and hydrogen bonding is of some influence on these conformational equilibria. A 2,6-disubstituted derivative prefers exclusively the *cis*-O-in-di-eq conformation **47** (93NKK850).

## D. 1,4-Dioxanes

As a semirigid model (77JCP2874), quantum-chemical AM1 and PM3 calculations (90JST179), and many NMR studies (to be discussed later) claim the chair conformation to be also that preferred for 1,4-dioxane. From dipole moment measurements, the participation of the boat conformer was suggested (76BSF1649, 76CR11; 77CR869).

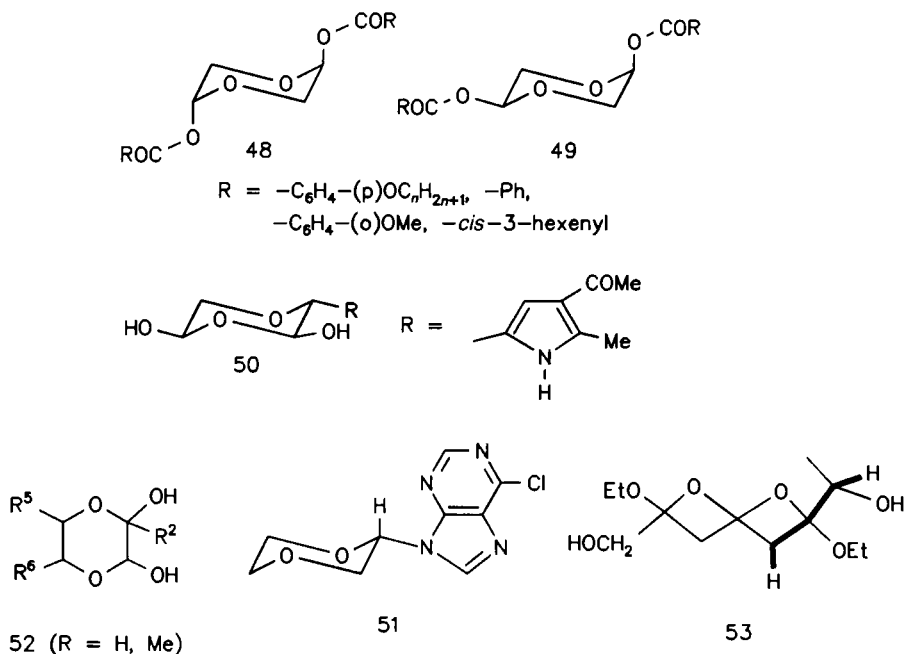
Only a few 1,4-dioxane derivatives monosubstituted in position 2, were studied (Table XI). Cl and OR substituents, in agreement with the anomeric effect, prefer the axial orientation; O-*t*Bu and OSiMe<sub>3</sub>, because of their steric bulk, destabilize the axial conformer and reduce the anomeric effect [68ZOR1498; 69ZOR(5)158]. The same is true for the *trans*-2,3- and *trans*-2,5-di(RO)-1,4-dioxanes; for groups R = Me, *i*Pr, *i*Bu, Ph, Ph-*p*NO<sub>2</sub>, Ac, more than 90% of the diaxial conformation was found (83TL3959; 84T2011; 85T3785). Substituents R = OSiMe<sub>3</sub>, Si-*t*Bu, and Ph-*O, O'*-di-Me, for the same reasons as just mentioned, shift the equilibrium more to the diequatorial conformation (79JOC2274; 79NJC145; 85T3785; 86AG289; 87JA1486). The solvent dependence of the conformational equilibria were also studied; the dipole moments of the two conformers proved to be strongly influential. The results are discussed in terms of combined anomeric and *gauche* interactions (84T2011; 86AG289; 87JA1486). The X-ray structure of *trans*-2,5-di-O-*t*Bu-1,4-dioxane and *ab initio* calculations corroborate the suggestions (87JA1486).

TABLE XI  
CONFORMATIONAL ENERGIES (FREE ENERGY DIFFERENCES  $-\Delta G^\circ$ ) OF  
SUBSTITUTED 1,4-DIOXANES

Substituent	Solvent	$-\Delta G^\circ/\text{kcal mol}^{-1}$	Ref.
2-Cl	CD <sub>3</sub> CN	-3	68ZOR1498; 69ZOR158
2-OCOMe	CD <sub>3</sub> CN	-2.3	68ZOR1498; 69ZOR158
	CCl <sub>4</sub>	-1.7	68ZOR1498; 69ZOR158
2-OMe	CD <sub>3</sub> CN	-0.59	68ZOR1498; 69ZOR158
	CCl <sub>4</sub>	-0.45	68ZOR1498; 69ZOR158
2-OEt	CD <sub>3</sub> CN	-0.59	68ZOR1498; 69ZOR158
	CCl <sub>4</sub>	-0.50	68ZOR1498; 69ZOR158
2-O- <i>n</i> Bu	CD <sub>3</sub> CN	-0.47	68ZOR1498; 69ZOR158
	CCl <sub>4</sub>	-0.39	68ZOR1498; 69ZOR158
2-O- <i>t</i> Bu	CD <sub>3</sub> CN	+0.07	68ZOR1498; 69ZOR158
	CCl <sub>4</sub>	+0.14	68ZOR1498; 69ZOR158
2-O-SiMe <sub>3</sub>	CDCl <sub>3</sub>	0.53	84T2011
2-purinyI <b>51</b>	CDCl <sub>3</sub>	0.14	75TL1553
	CD <sub>3</sub> CN	0.12	75TL1553
<i>trans</i> -2,3-di-OR <sup>a</sup>	CDCl <sub>3</sub>	> -1.87	84T2011
<i>trans</i> -2,3-di-OSiMe <sub>3</sub>	CDCl <sub>3</sub>	0.44	87T2011
<i>trans</i> -2,3-di-O- <i>t</i> Bu	CDCl <sub>3</sub>	0.71	84T2011
	CDCl <sub>3</sub>	-0.01	83TL3959
<i>trans</i> -2,3-di-O- <i>i</i> Bu	CDCl <sub>3</sub>	-1.29	83TL3959
<i>trans</i> -2,3-di-O- <i>i</i> PrBu	CDCl <sub>3</sub>	-1.19	83TL3959
<i>trans</i> -2,3-di-O-C <sub>6</sub> H <sub>4</sub> - <i>p</i> NO <sub>2</sub>	CDCl <sub>3</sub>	-2.29	85T3785
<i>trans</i> -2,3-di-O-C <sub>6</sub> H <sub>3</sub> - <i>O</i> , <i>O'</i> -di-Me	CDCl <sub>3</sub>	-0.38	85T3785
<i>trans</i> -2,5-di-OR <sup>a</sup>	CDCl <sub>3</sub>	> -1.87	84T2011
<i>trans</i> -2,5-di-OSiMe <sub>3</sub>	CDCl <sub>3</sub>	0.07	84T2011
<i>trans</i> -2,5-di-O- <i>t</i> Bu	CDCl <sub>3</sub>	0.02	84T2011
<i>trans</i> -2,5-di-OH	Acetone- <i>d</i> <sub>6</sub>	-0.24	81MI1
<i>trans</i> -2,3-di-SMe	CDCl <sub>3</sub>	-0.53	90TL2755
<i>trans</i> -2,3-di-SEt	CDCl <sub>3</sub>	-0.69	90TL2755
<i>trans</i> -2,3-di-S- <i>i</i> Pr	CDCl <sub>3</sub>	-0.76	90TL2755
<i>trans</i> -2,3-di-S- <i>t</i> Bu	CDCl <sub>3</sub>	-1.03	90TL2755
<i>trans</i> -2,3-di-SC <sub>12</sub> H <sub>25</sub>	CDCl <sub>3</sub>	-0.69	90TL2755
<i>trans</i> -2,3-di-SPh	CDCl <sub>3</sub>	-1.38	90TL2755
<i>trans</i> -2,3-di-S-C <sub>6</sub> H <sub>4</sub> - <i>p</i> Me	CDCl <sub>3</sub>	-1.19	90TL2755
<i>trans</i> -2,3-di-S-C <sub>6</sub> H <sub>4</sub> - <i>p</i> Cl	CDCl <sub>3</sub>	-1.24	90TL2755

<sup>a</sup> R = Me, Ph, Ac.

The corresponding *trans*-2,5-di-OH-1,4-dioxane on the most recent evidence also slightly prefers the diaxial conformation (81MI1; 86MI2), in contrast to previous IR studies at 50°C and <sup>1</sup>H NMR studies at lower magnetic fields [71JCS(B)1352; 76JST235]. Substituted benzo-carbonyl-oxy substituents in these positions also completely adopt the diaxial orientation **48** (Scheme 22); the corresponding dicarboxylic esters, however, are com-



SCHEME 22

pletely in the 2,5-diequatorial conformation **49** (86MI1; 89MI1). The latter orientation is in line with the liquid-crystalline properties of these compounds (89MI1; 91MI1).

A bulky 2-pyrrole moiety in equatorial position 2 forces hydroxy substituents in positions 3 and 5 into the diequatorial orientation, because only this stereochemistry **50** (Scheme 22) could be detected (83AQ18). However, the bulky purine moiety only slightly prefers the equatorial orientation **51** (see Table XI and Scheme 22) (75TL1553).

In a number of methyl-substituted 2,5-di-OH-1,4-dioxane derivatives, the strongly equatorially predominating methyl group dominates the present conformational equilibria [78OMR152; 81MI1; 83SA(A)569]. In addition, the equilibrium constants of the configurational and conformational equilibria of the 2,3-di-OH-1,4-dioxane derivatives **52** were determined (78OMR152).

A few 2,2,5,5-tetrasubstituted 1,4-dioxane derivatives were reported; OR substituents tend to adopt, because of the anomeric effect, axial positions [94AX(C)625, 94MI1]. By contrast, *trans*-2,5-di-OCOOR- and 2,5-di-CH<sub>2</sub>COOR-1,4-dioxane derivatives ( $R = \text{aryl, alkyl}$ ) (84JHC1197), 2-(1'-uracil)-6-CH<sub>2</sub>OH-1,4-dioxane (92MI2), and 2,5-di-OH-3,6-di-CH<sub>2</sub>OH-1,3-





along with the steric bulk of the SR substituents. The C—S bond, which is larger than the C—O bond, was identified as the major reason for this divergent behavior, and the sequence of the  $-\Delta G^\circ$  values was discussed in terms of repulsive *gauche* and stabilizing *exo*-anomeric interactions (90TL2755). The dithiuronium dichloride substituents **55** [ $R = C(NH_2) = NH_2^+ Cl^-$ ] were also in a diaxial orientation [76JCS(P1)121].

From the mixture of the five isomers of 2,3,5,6-tetra-Me-1,4-dioxane, two (**56**, **57**) were isolated and assigned by  $^1H$  NMR spectroscopy (73CPB1103).

The structure of some complexes  $[Cu_2(COPh)_2 4L] \cdot 2L$  (79MI5),  $Sm(H_2O)_9 Br_3 L_2$  (85MI1), and  $SnCl_2 L_2$  [76JCS(D)1782] ( $L = 1,4$ -dioxane) were reported; the 1,4-dioxane ring proved generally to exist in a chair conformation. The conformation of the organoiron complexes **58**, **59** [ $F_p = \eta-C_5H_5$ ] $Fe(CO)_2$  (88MI1) (Scheme 24) were studied in more detail by both NMR spectroscopy and X-ray analysis; the low conformational energy of the extremely bulky  $F_p$  substituent is a consequence of the length of the C—Fe bond.

The chair conformation of the 1,4-dioxane ring is also preserved in the channel of the hexakis( $\beta$ -naphthylthio)benzene-1,4-dioxane host–guest complex (82TL4131).

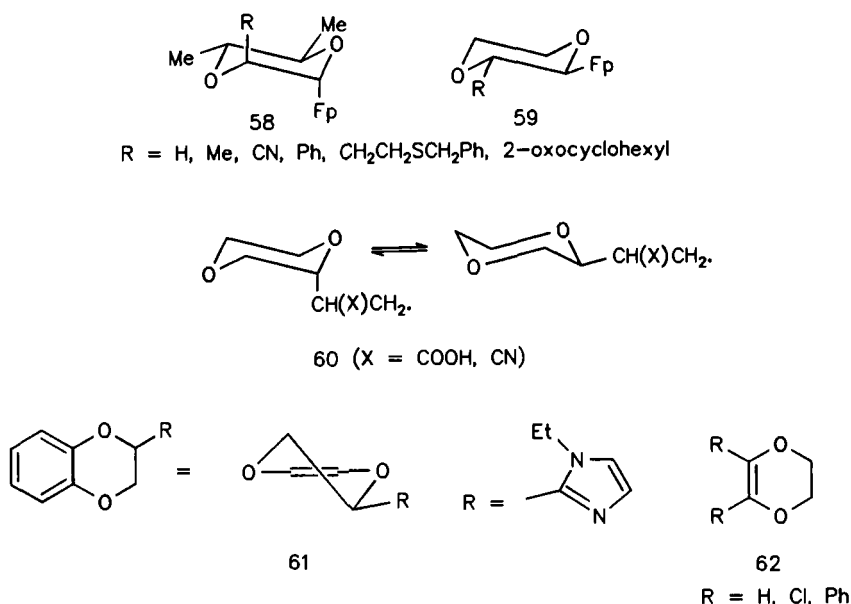
The EPR spectra of the  $\alpha$ -substituted 2-ethyl radical of 1,4-dioxane **60** (Scheme 24) were explained in terms of the presence of the radical group in both axial and equatorial orientations, the equilibrium being slow on the EPR timescale at room temperature (89MRC782).

Benzo-1,4-dioxane derivatives **61** exist in a half-chair conformation with the substituent R in an equatorial position ( $R = CH_2NR_2$  [81MI2],  $R = CBr_2Me$  [88AX(C)189],  $R = 2$ -imidazolyl [93JST(285)235]); 2,3-dihydro-1,4-dioxine **62** (82OMR92) and the corresponding radical cations (89CJC1784) prefer the same half-chair conformation.

Finally, some extensively substituted 2-OH,2-Cl-1,4-dioxanes (in a chair conformation) (93T10511) and 2,3-di-Me-1,4-dioxanes (in a half-chair conformation) (75OMR177) were reported.

## E. Trioxanes

The molecular structure of *s*-trioxane (1,3,5-trioxane) has been studied by microwave (80JSP165), vibrational (77JPC32; 79CJC711), NMR (in the liquid crystal phase) (95MRC831), and X-ray spectroscopy [69AX(B)1191]. These studies all indicated that the molecule exists predominantly in the chair conformation of  $C_{3v}$  symmetry with the methylene protons tilted from the threefold axis of symmetry by  $-2.1^\circ$ , in good agreement with the results of quantum chemical *ab initio* calculations at the 6-31G\* level (95MRC831).



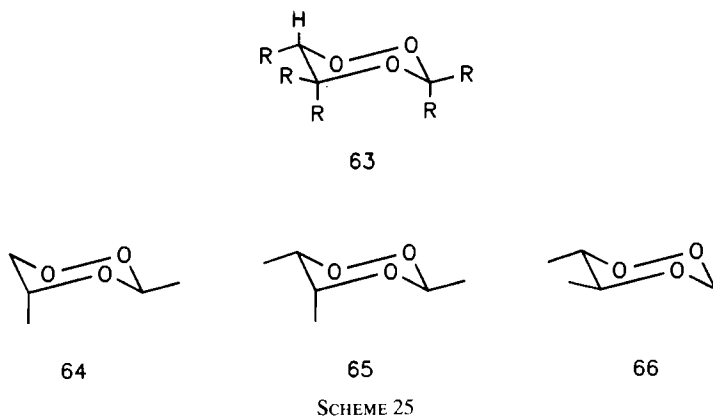
SCHEME 24

Also for 1,2,4-trioxane, from MM3 calculations, a structure close to a chair with the protons and substituents in axial and equatorial positions, respectively, was suggested [92JCS(CC)1689]. The substituted derivatives **63** (Scheme 25) have substituents R [Me, *i*Pr,  $\text{CH}_2\text{HgBr}$ ,  $\text{CH}(\text{HgBr})\text{Me}$ ] in an equatorial position (all in agreement with standard conformational principles), and only in **64–66** were axial methyl substituents reported, based on NOE measurements and  $^1J_{\text{C-H}}$  coupling constants [92JCS(CC)1689].

## F. Tetroxanes

Photoelectron spectra (79LA1373), detailed NMR studies (68DOK1122; 70T3, 70ZSK770; 71T3629), and X-ray structures [67CB2242; 88JC-S(CC)465; 90AX(C)2476] prove *s*-tetroxane (1,2,4,5-tetroxane) to preferentially adopt the chair conformation. Some semiempirical quantum-chemical calculations [AM1, PM3 (94JST315), and MINDO/3 (86JST7)] for *s*-tetroxane were carried out; the latter, in opposition to the experiment, find a twisted boat to be the preferred conformer.

3,3,5,5-Tetramethyl-1,2,4,5-tetroxane (67CB2242), 3,6-di- $\text{C}_9\text{H}_{19}$ - (in a 3,6-diequatorial orientation where the alkyl chains are in an all-*trans*-confor-



mation) [90AX(C)2476], and 3,6-di-OMe-1,2,4,5-tetroxane (in a diaxial orientation due to the anomeric effect) [88JCS(CC)465] were studied by X-ray analysis in the solid state. The last compound was also the object of a detailed proton NMR study [88JCS(CC)465]; in acetone- $d_6$  at  $-80^\circ\text{C}$ , a conformational equilibrium  $ax,ax \rightleftharpoons eq,eq$ , (75%:25%;  $\Delta G^\circ = 0.42 \text{ kcal mol}^{-1}$ ) with a preference for the diaxial conformer was found. The anomeric effect also dominates the conformational equilibrium of 2-OMe-1,2,4,5-tetroxane; the axial conformer was found (95JST25), in agreement with the X-ray structure [88JCS(CC)465].

### G. Cyclic $\text{O}_6$

By means of *ab initio* calculations at the 6-31G\* level, the conformation and the spectroscopic and structural properties of cyclic  $\text{O}_6$  have been calculated (88JPC959; 93JPC4023); the chair was the most stable conformation, the twist conformation ( $15.9 \text{ kcal mol}^{-1}$ ) and the boat conformation ( $17.5 \text{ kcal mol}^{-1}$ ) being higher in energy.

## IV. Ring Inversion Barriers

The barriers to ring inversion of the basic O-containing saturated six-membered rings have been reviewed (74FCF139; 75MI1; 85MI3). The free energies of activation,  $\Delta G^\ddagger$ , are included in Table XII. The energy barriers of a number of substituted 1,3-dioxanes (75MI41) and some spiro-substituted 1,3-dioxanes (74FCF139) are not considered further here, but the

TABLE XII  
BARRIERS TO RING INTERCONVERSION [ $\Delta G^\ddagger$  (kcal mol<sup>-1</sup>)] OF OXANE DERIVATIVES

	Solvent	$-\Delta G^\ddagger$	Ref.
Oxane	CD <sub>3</sub> OD/CHClF <sub>2</sub>	10.3	73JA4634
2,2-di-OMe-oxane	CS <sub>2</sub>	8.68	84JCS(CC)333
2-cyclo-N(CH <sub>2</sub> ) <sub>2</sub> -oxane	CS <sub>2</sub>	9.4(8.9)	83JCS(P2)249
2,2,6,6-tetra-Me-1,2-dioxane	CS <sub>2</sub>	14.3	66SA623
1,3-Dioxane	Acetone- <i>d</i> <sub>6</sub>	9.9	68ACSA1705
5,5-di-CH <sub>2</sub> Cl-1,3-dioxane	Toluene- <i>d</i> <sub>8</sub>	11.3	87KGS607
5,5-di-CH <sub>2</sub> I-1,3-dioxane	Toluene- <i>d</i> <sub>8</sub>	11.95	87KGS607
1,4-Dioxane <sup>a</sup>	CDCl <sub>2</sub> /CHClF <sub>2</sub>	9.7	71JCS(CC)1558
5,5,6,6-tetra-Me-1,2,4-trioxane	CDCl <sub>3</sub>	12.2	93JCS(P2)1927
3,3,5,5,6,6-tetra-Me-1,2,4-trioxane	CDCl <sub>3</sub>	12.3	93JCS(P2)1927
3,3-(CH <sub>2</sub> ) <sub>5</sub> -5,5,6,6-tetra-Me-1,2,4-trioxane	CDCl <sub>3</sub>	11.6	93JCS(P2)1927
3,3(spiro[2.2]adamantyl-5,5,6,6-tetra-Me-1,2,4-trioxane	CDCl <sub>3</sub>	11.6	93JCS(P2)1927
3,3,6,6-tetra-Me-1,2,4,5-tetroxane	CCl <sub>4</sub>	15.3	70T3
		15.0	66JA526
3,3,6,6-tetra-Et-1,2,4,5-tetroxane	CCl <sub>4</sub>	14.1	71T3629
3,6-di-Me-3,6-di-Et-1,2,4,5-tetroxane	CCl <sub>4</sub>	15.0	71T3629
3,6-di-Me-3,6-di-CH <sub>2</sub> Ph-1,2,4,5-tetroxane	CDCl <sub>3</sub>	14.6	71T3629
3,6-di-Me-3,6-di-CH <sub>2</sub> Br-1,2,4,5-tetroxane	CDCl <sub>3</sub>	12.7	71T3629
3,6-di-Me-3,6-di-CH <sub>2</sub> Cl-1,2,4,5-tetroxane	CDCl <sub>3</sub>	12.6	71T3629

<sup>a</sup> Determined from hexadeutero-1,4-dioxane; from the nondeuterated derivative the single line remained sharp down to  $-150^\circ\text{C}$ ; in liquid crystal solution:  $\Delta H^\ddagger = 9.64$  kcal mol<sup>-1</sup>;  $\Delta S^\ddagger = 0.1$  e.u. (83JMR354).

$\Delta G^\ddagger$  values of oxane derivatives not covered by the mentioned references are given in Table XII and are briefly discussed.

Perrin and Nunez [84JCS(CC)333] determined the barrier to inversion of 2,2-di-OMe-oxane ( $\Delta G^\ddagger = 8.7$  kcal mol<sup>-1</sup>) and found, in opposite to Deslongchamps (75CJC3029), the anomeric effect to reduce the barrier to conformational change by 1.4–2.1 kcal mol<sup>-1</sup>. Anderson *et al.* [93JCS(P2)1927] studied the ring interconversion of four 1,2,4-trioxanes and found the corresponding barriers to ring inversion to be dependent on both the rotation about individual bonds and the overall flatness of the ground-state ring conformation, two effects operating in opposite directions and too complicated to elucidate. In addition, the inductive effect of substituents (70T3; 71T3629) and hydrogen bonding proved to influence the barrier to ring inversion (68DOK1122; 70ZSK770).

The 1,4-dioxane-2-radical undergoes chair  $\rightleftharpoons$  chair ring flipping with an energy of activation of  $E_a = 6.7 \text{ kcal mol}^{-1}$  [74JCS(P2)1033].

The ring interconversion of 1,2-, 1,3-, 1,4-ox-4-enes, and *exo*-methylene-1,3-dioxanes has been reviewed by Oki (85MI3).

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# Heteropentalenes with a Fused Imidazole or 1,2,4-Triazole Ring and One Bridgehead Nitrogen Atom

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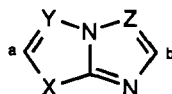
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## I. Introduction

In this article some heterocyclic (5,5)-fused systems with one bridgehead nitrogen atom will be reviewed. The survey given here is limited to those heterocycles that contain 10  $\pi$ -electrons and where atoms a and b are carbon (Scheme 1).

Compounds of this type have been reviewed occasionally [61HC(15)203; 77HC(30)1; 84CHEC(6)973; 96CHEC2(8)288]. Interest in this field of heterocycles emerged not only because of their biological properties, but also because of their suitability as new materials, such as liquid crystals [88JOU172, 88JOU179, 88JOU1177, 88ZOR192, 88ZOR199, 88ZOR1306; 90MI3; 93MI8; 96UP1]. The main emphasis in this article is directed to the synthesis and reactions of these heterocycles.



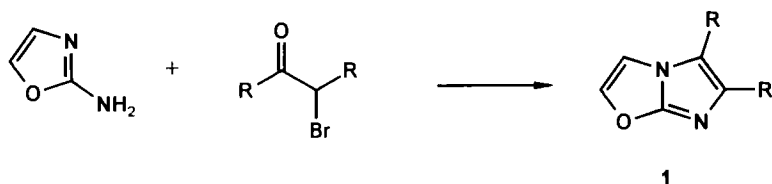
X	Y	Z	
O	C	C	Imidazo[2,1- <i>b</i> ]oxazoles
O	N	C	Imidazo[2,1- <i>b</i> ][1,3,4]oxadiazoles
O	C	N	Oxazolo[3,2- <i>b</i> ][1,2,4]triazoles
O	N	N	1,2,4-Triazolo[5,1- <i>b</i> ][1,3,4]oxadiazoles
S	C	C	Imidazo[2,1- <i>b</i> ]thiazoles
S	N	C	Imidazo[2,1- <i>b</i> ][1,3,4]thiadiazoles
S	C	N	Thiazolo[3,2- <i>b</i> ][1,2,4]triazoles
S	N	N	1,2,4-Triazolo[5,1- <i>b</i> ][1,3,4]thiadiazoles

SCHEME 1

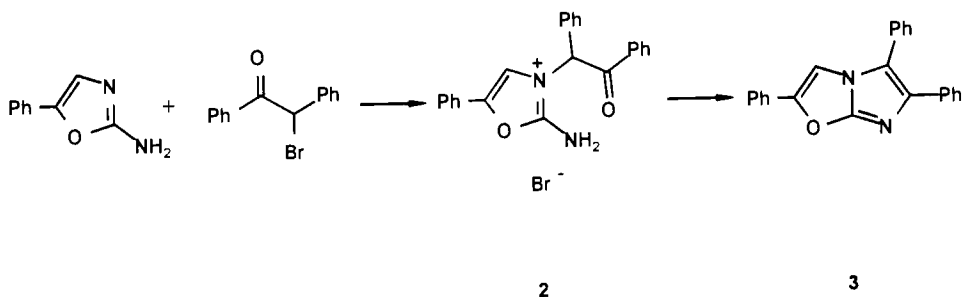
## II. Imidazo[2,1-*b*]oxazoles

### A. SYNTHESIS

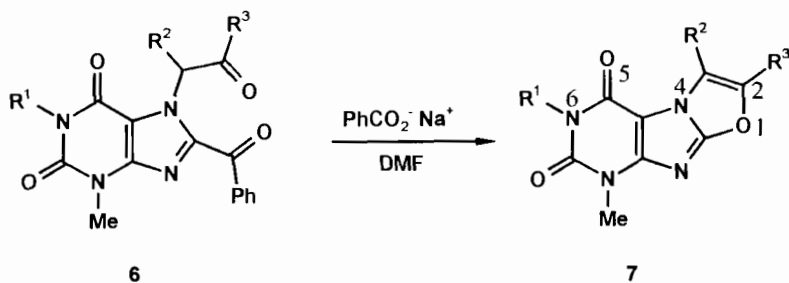
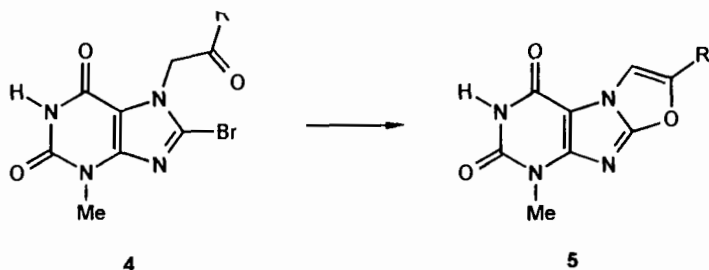
The first report of a synthesis of imidazo[2,1-*b*]oxazoles was in 1967 (67USP345592). The reaction of 2-amino-1,3-oxazole with an  $\alpha$ -bromod-*esoxybenzoin* yields **1** (mp 227°C).



The tetraphenyl derivative was prepared similarly (DMF/EtOH, 4.5h) (75ZC267). The cyclization can also be done in two steps. *N*-Alkylation of 2-amino-5-phenyloxazole with desyl bromide yields **2**, which on treatment with base (EtOH/KOH, 2.5 h, reflux) gives **3** (75ZC267).

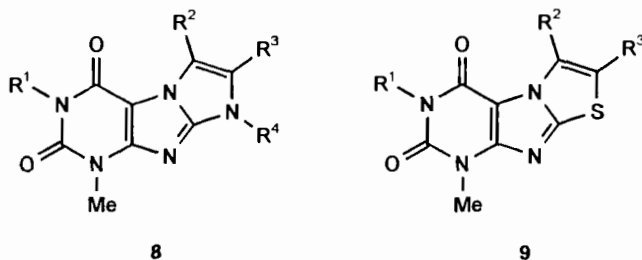


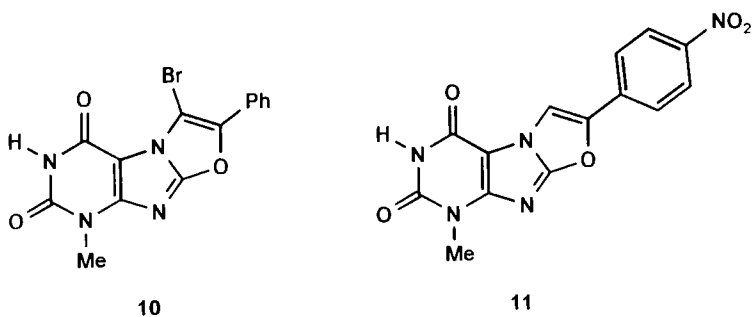
Condensed derivatives have also been reported. Cyclization of **4** in formamide yields **5** (69%, mp > 330°C (86KGS1133). Similarly, treatment of **6** with sodium benzoate (DMF) gives **7**.



## B. REACTIONS

Only a few reactions of imidazo[2,1-*b*]oxazoles have been reported. On treatment of compounds **7** with amines or sodium sulfide ( $\text{Na}_2\text{S} \cdot 9 \text{H}_2\text{O}$ ) the corresponding aza (**8**,  $\text{R}^4 = \text{H, Me, Ph, PhCH}_2$ ) and thio analogs (**9**) are obtained (88KGS534). Compounds of type **7** with  $\text{R}^1 = \text{H}$  can be alkylated at N-6 (e.g., with ethyl iodoacetate). Bromination of **7** ( $\text{R}^2 = \text{H, R}^3 = \text{Ph}$ ) occurs at position 3 and gives **10**; nitration takes place on the side chain, resulting in the formation of **11** (90KGS1396).

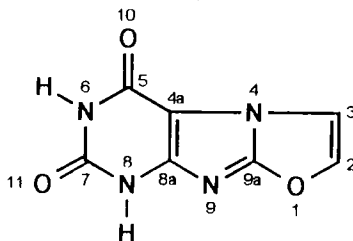




### C. STRUCTURAL AND THEORETICAL STUDIES

Structural and theoretical studies on these systems are scarce. A molecular diagram (bond orders, electron densities) of 2-phenyloxazole[3,2-*f*]xanthine has been reported (HMO method with standard parameters

TABLE I  
BOND DISTANCES OF OXAZOLO[3,2-*f*]XANTHINE **12** (MNDO, AM1, PM3, AB INITIO, DFT)  
(VALUES IN Å) <96UP2>



**12**

Method	$r_{12}$	$r_{1,9a}$	$r_{23}$	$r_{34}$	$r_{4,4a}$	$r_{4,9a}$	$r_{4a,5}$	$r_{4a,8a}$
MNDO	1.390	1.347	1.384	1.413	1.401	1.420	1.451	1.420
AM1	1.423	1.385	1.379	1.396	1.388	1.433	1.449	1.445
PM3	1.399	1.371	1.368	1.419	1.407	1.408	1.446	1.413
6-31G*	1.378	1.316	1.328	1.390	1.392	1.329	1.428	1.367
DFT <sup>a</sup>	1.392	1.343	1.352	1.392	1.391	1.362	1.432	1.393

Method	$r_{56}$	$r_{5,10}$	$r_{67}$	$r_{78}$	$r_{7,11}$	$r_{8,8a}$	$r_{8a,9}$	$r_{9,9a}$
MNDO	1.430	1.225	1.413	1.417	1.227	1.383	1.393	1.354
AM1	1.407	1.242	1.407	1.413	1.249	1.380	1.416	1.364
PM3	1.434	1.221	1.428	1.428	1.225	1.398	1.404	1.364
6-31G*	1.395	1.198	1.381	1.374	1.193	1.365	1.351	1.305
DFT <sup>a</sup>	1.415	1.223	1.399	1.394	1.217	1.373	1.366	1.322

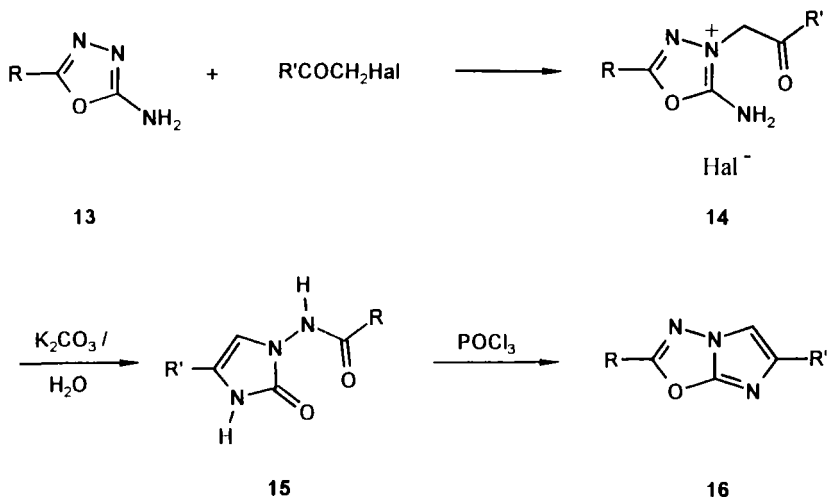
<sup>a</sup> Becke3LYP/6-31G\*.

(90KGS1396). The results of a geometry optimization of **12** using semiempirical [MNDO, AM1, PM3 (90MI1)], *ab initio* (93MI1), and density functional theoretical (DFT) studies (95MI1) are given in Table 1 (96UP2). As in the case of other heterocycles [96MI1] DFT methods seem reliable in predicting the geometry of these compounds (see also Sections VI and VII).

### III. Imidazo[2,1-*b*][1,3,4]oxadiazoles

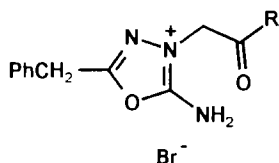
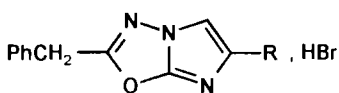
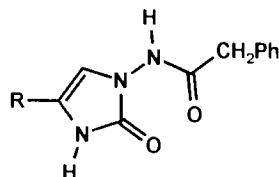
#### A. SYNTHESIS

A very convenient and broad approach to imidazo [2,1-*b*][1,3,4]oxadiazoles starts with 5-substituted 2-amino-1,3,4-oxadiazoles [**13**; for a review see, e.g., Hetzheim (94HOU526)]. Treatment of **13** with  $\alpha$ -halo ketones yields the corresponding oxadiazolium salts **14**, which rearrange in a slightly basic medium to give 1-acylamino-4-substituted imidazol-2-ones **15** (62ZC152; 64CB1031). These compounds can also be prepared from *N,N'*-bisacylhydrazines. Cyclization with phosphorus oxychloride (30–45 min, reflux) gives imidazo[2,1-*b*][1,3,4]oxadiazoles **16** (62ZC153; 70CB272; 72BSF3968).



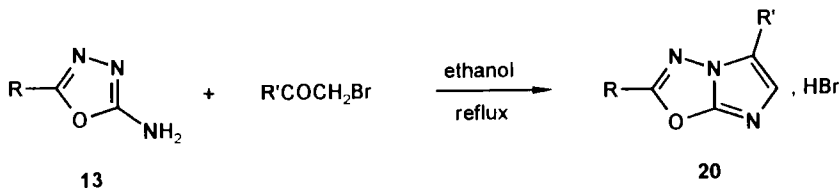
There is an early report by Westphal and Henklein that oxadiazolium salts **17** cyclize in boiling water to give salts of imidazo[2,1-*b*][1,3,4]oxadiazoles (**18**), which on treatment with sodium hydroxide yield the corresponding free bases (69ZC25). But Hetzheim notes that these results are in error

(69ZC337).<sup>1</sup> The substances isolated by Westphal and Henklein were in fact 1-acylaminoimidazolones **19**.

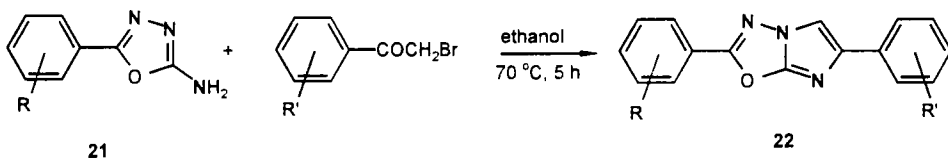
**17****18****19**

R = aryl

Treatment of 2-amino-1,3,4-oxadiazoles **13** with bromoketones in boiling ethanol gives imidazo[2,1-*b*][1,3,4]oxadiazoles **20** directly (isolated as salts (82JIC1170)).<sup>2</sup>

**13****20**

Alkylation of 2-amino-5-(alkyl, aryl, hetaryl)-1,3,4-oxadiazoles is said to occur at the ring N atom (N-3) (94HOU526), but this report remains doubtful. In addition, as others have pointed out, the very low basicity of imidazo[2,1-*b*][1,3,4]oxadiazoles precludes the isolation of hydrohalides of type **20**. 2,6-Diaryl-imidazo[2,1-*b*][1,3,4]oxadiazoles **22** can be obtained directly by treatment of 2-amino-5-aryl-1,3,4-oxadiazoles **21** with phenacyl-bromides in ethanol [reflux in a water bath at 70°C (!) for 5 h] (84MI1).

**21****22**

R = H, 2-Cl, 4-Cl, 4-OMe;

R' = H, 4-OMe, 4-Me, 4-Cl, 4-Br

<sup>1</sup> The results given in Preston [86HC(46)77] should be revised.

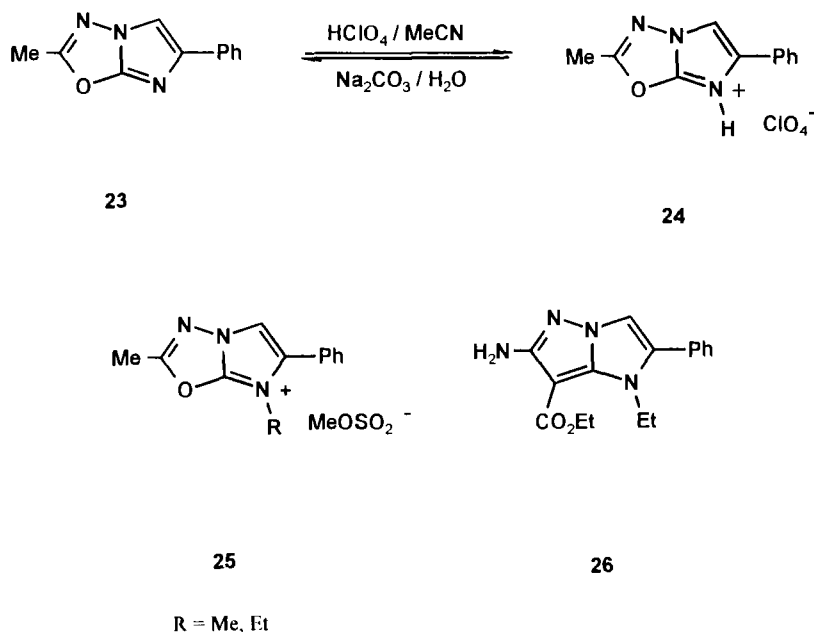
<sup>2</sup> There are some inconsistencies in this article that preclude definitive statements.



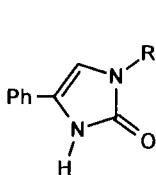
The melting points for **22** ( $R = H$ ,  $R' = 4\text{-OMe}$ ,  $4\text{-Me}$ ,  $4\text{-Cl}$ ,  $4\text{-Br}$ ) given by these authors differ considerably from those reported by Hetzheim and Beyer (70CB272).

## B. REACTIONS

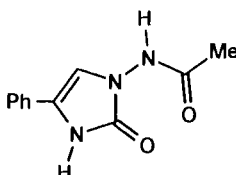
Only a few reactions of imidazo[2,1-*b*][1,3,4]oxadiazoles have been reported. The basicity of these compounds is rather low; hydrohalides cannot be isolated (69ZC337). Protonation of **23** with strong acids occurs at position 7, giving, for example, **24** (mp  $212^\circ\text{C}$  with explosion!). With aqueous base **24** is converted back to **23** (72BSF3968). On alkylation of **23** the quaternary salts **25** are obtained (72BSF3968). Reaction of **25** ( $R = \text{Et}$ ) with ethyl cyanoacetate ( $\text{Et}_3\text{N}/\text{EtOH}$ ) yields **26**, albeit in low yield (3.8%) (72BSF3968).



In line with expectations strong acids and bases cleave the oxadiazole ring. After treatment of **23** with 48% HBr an imidazolone-2 (**27**,  $R = H$ ) is isolated; with conc. HCl **27** ( $R = \text{NH}_2$ ) is obtained. Treatment with dilute base (8% KOH) yields compound **28**. Compound **27** ( $R = \text{NH}_2$ ) is also isolated when **23** is treated with hydrazine hydrate.



27



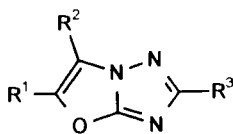
28

R = H, NH<sub>2</sub>

The stability of imidazo[2,1-*b*][1,3,4]oxadiazoles depends to a considerable extent on the substituents (70CB272).

#### IV. Oxazolo[3,2-*b*][1,2,4]triazoles

The parent ring (**29**, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> = H) and derivatives thereof seem to be unknown. Only hydrogenated oxazolo[3,2-*b*][1,2,4]triazoles have been reported (see, e.g., 74KGS997; 76KGS1281; 81KGS1403, 81LA1433; 90T3211).

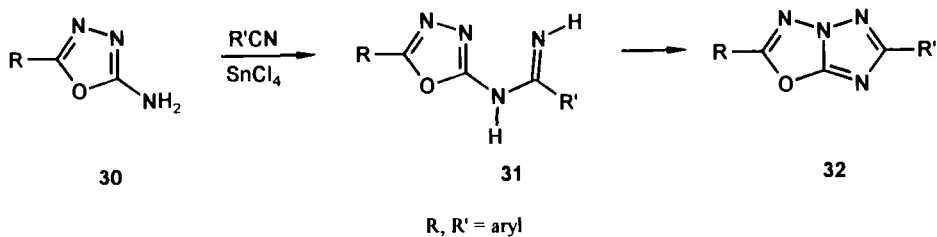


29

#### V. 1,2,4-Triazolo[5,1-*b*][1,3,4]oxadiazoles

##### A. SYNTHESIS

1,2,4-Triazolo[5,1-*b*][1,3,4]oxadiazoles (**32**) seem to have been described only once. They are prepared as crystalline substances by treatment of 2-amino-1,3,4-oxadiazoles (**30**) with nitriles in the presence of anhydrous stannic chloride (230–240°C, 10 h) and subsequent dehydrogenation of the resulting amidines **31** with lead tetra-acetate in 30–62% yield [95IJC(B)644].



## VI. Imidazo[2,1-*b*]thiazoles

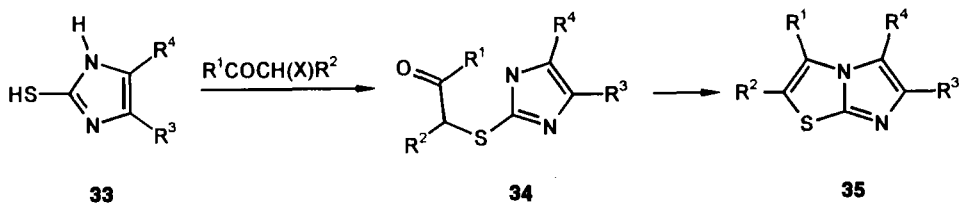
Imidazo[2,1-*b*]thiazoles have been known since 1936 (36CB1650), but only recently has there been much interest in this class of compounds. These substances not only exhibit biological activity, but also seem to be interesting starting materials for the preparation of compounds with unique physical properties [(e.g., liquid crystals (96UP1)]. In the following articles, both the synthesis and the reactions and properties of these compounds are delineated.

### A. SYNTHESIS

Only a few methods are useful for the preparation of imidazo[2,1-*b*]thiazoles. These are comprehensively treated in this section, where preference is given to the most important examples. The relevant literature is reviewed from its beginning to the present.

#### 1. From Imidazoles

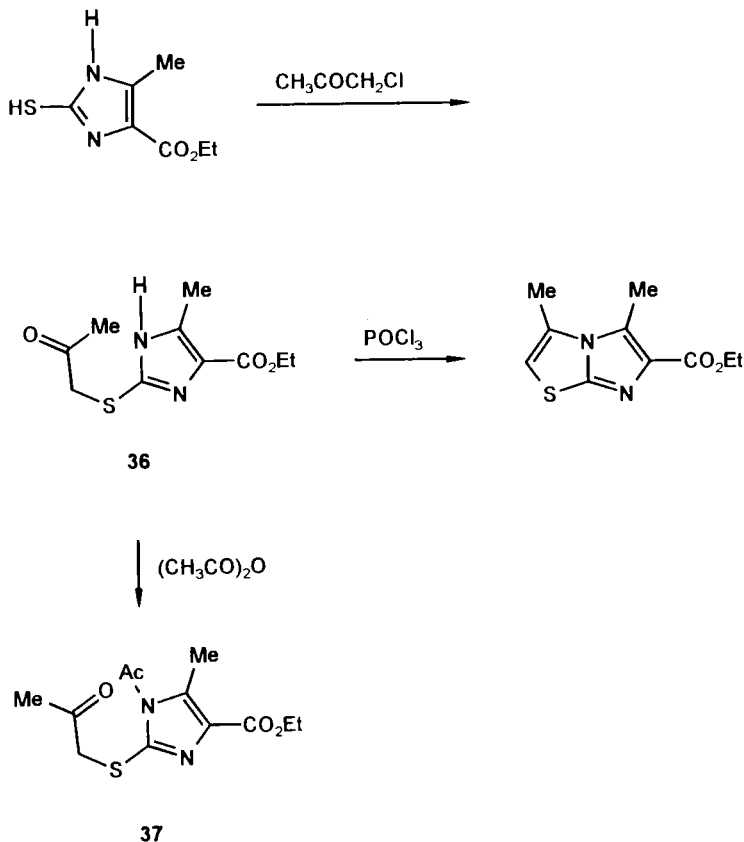
Treatment of 2-mercaptoimidazoles **33** with  $\alpha$ -halo ketones gives 2-(acyl-alkylthio)-imidazoles **34**, which can be cyclized to substituted imidazo[2,1-*b*]thiazoles **35** [86HC(46)77]. A one-step synthesis from **33** with  $\alpha$ -halo ketones is also successful.



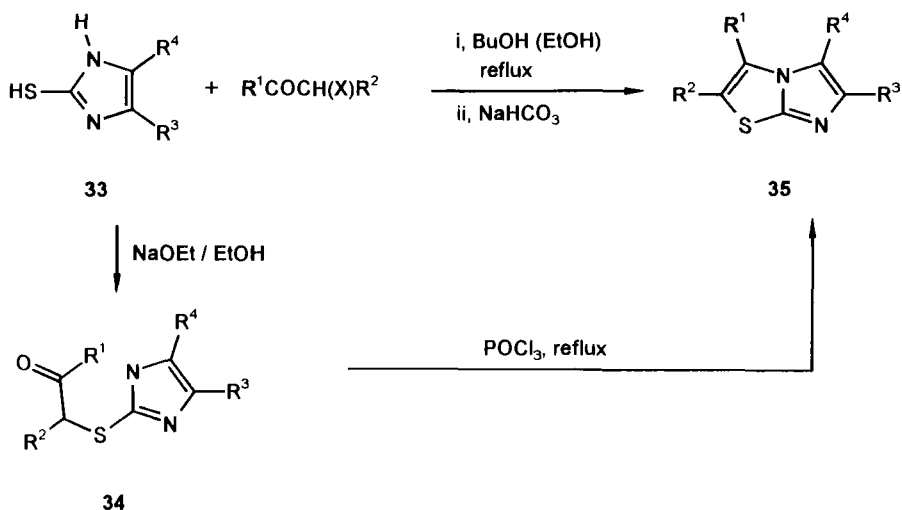
R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> = H, alkyl, hetaryl, alkoxycarbonyl etc.

X = Hal

Ochiai, who reported in 1936 the first synthesis of the imidazo[2,1-*b*]thiazole system (36CB1650), transformed ethyl 2-mercapto-5-methyl-imidazole-4-carboxylate with monochloroacetone into 2-(acylalkylthio)-imidazole **36**. Refluxing **36** in phosphorus oxychloride yields ethyl 3,5-dimethylimidazo[2,1-*b*]thiazole-6-carboxylate. No cyclization could be achieved by heating **36** in acetic anhydride because *N*-acylation (to **37**) inhibited further reaction to the bicyclic system.

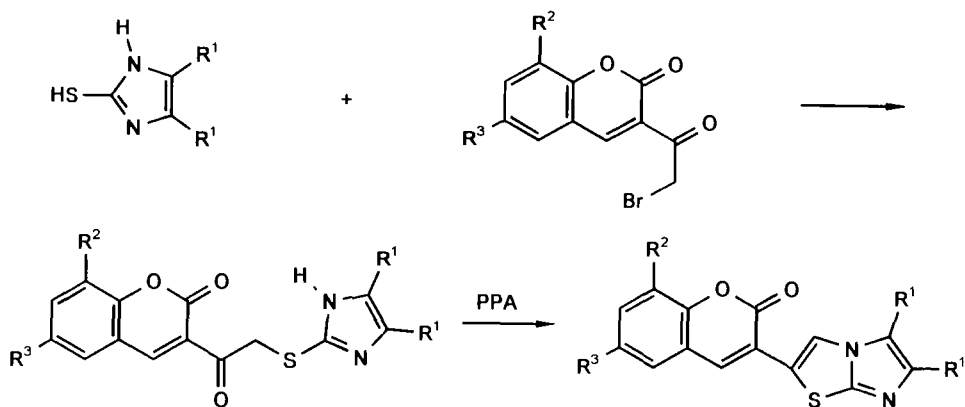


Russian authors investigated this important reaction type to prepare a wide range of aryl-, alkyl-, and acyl-substituted imidazo[2,1-*b*]thiazoles (70KGS508, 70KGS512; 71KGS389). Several 2-mercaptoimidazoles react with  $\alpha$ -halo ketones in one step directly to the bicyclic products **35** under reflux in butanol or ethanol followed by basification. Yields vary between 52 and 99%, but the two-step cyclization route requires isolation of the intermediates **34** and subsequent heating in phosphorus oxychloride.



$R_1$  to  $R_4$ : see Table II

Veerabhadraiah *et al.* (89SUL167) treated 4,5-disubstituted 2-mercaptoimidazoles with 3-( $\omega$ -bromoacetyl)coumarins and obtained ketones that on subsequent cyclization with PPA furnished 2,5,6-trisubstituted imidazo[2,1-*b*]thiazoles **38**.



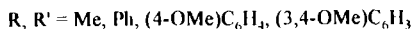
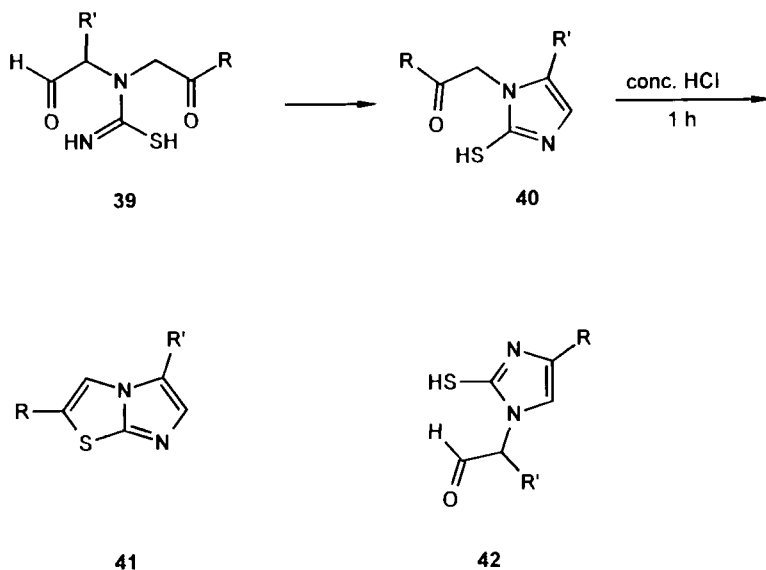
**38**

$R^1 = Ph, (4-OCH_3)C_6H_4$

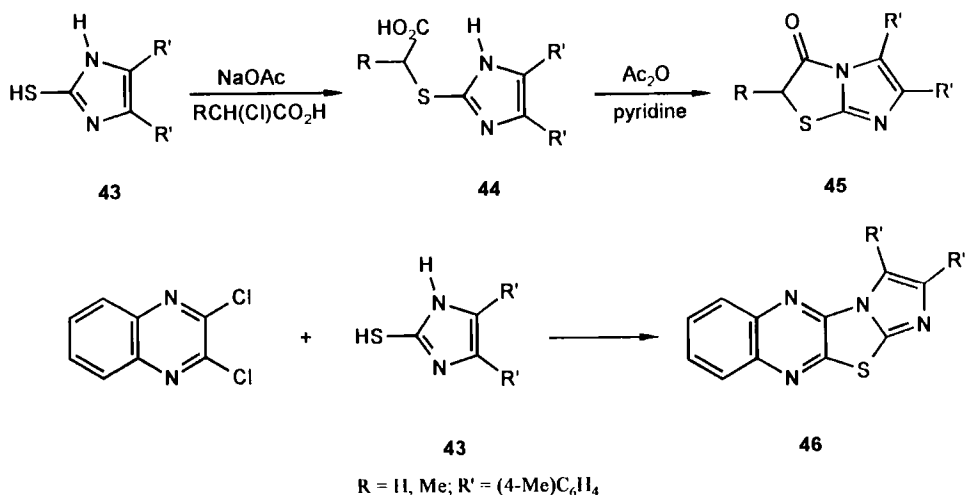
$R^2 = H, OMe, Br$

$R^3 = H, Br$

2,5-Disubstituted imidazo[2,1-*b*]thiazoles **41** have been prepared (55JCS1695; 57JCS566) by cyclization of 1,5-disubstituted 2-mercaptoimidazoles **40** in conc. hydrochloric acid. The latter compounds were synthesized via cyclization of the thiourea derivatives **39**. No aldehyde (**42**) was isolated from the reaction; obviously the thiourea cyclized more readily by reaction with the aldehyde than with the keto group.

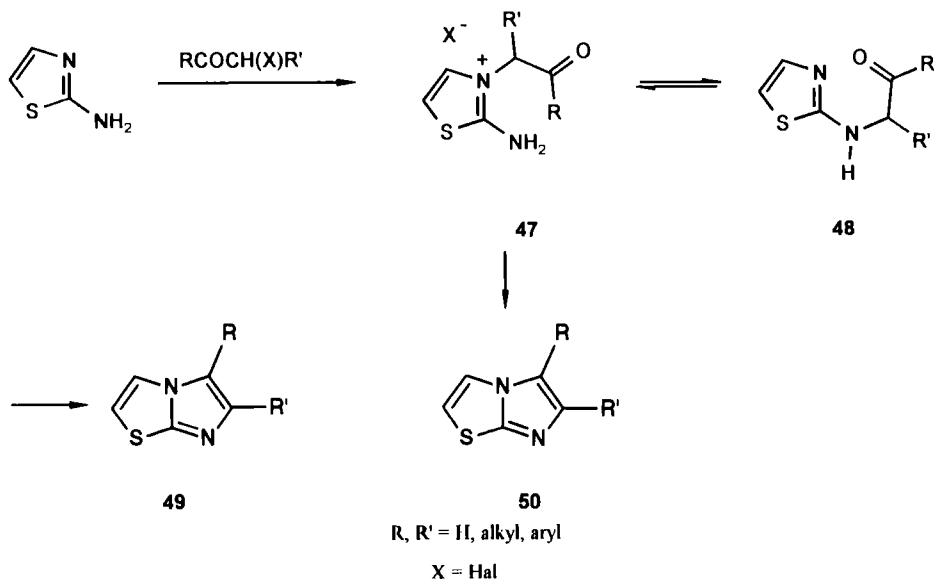


In another approach [88IJC(B)570], reaction of 2-mercapto-4,5-di-*p*-tolylimidazole **43** with  $\alpha$ -halo carboxylic acids enabled the synthesis of several imidazo[2,1-*b*]thiazoles. Acylative ring closure of 4,5-di-*p*-tolylimidazo-2-thioacetic acid (**44**, R = H) or 2-thiopropionic acid (**44**, R = Me) provides 5,6-di-*p*-tolylimidazo[2,1-*b*]thiazole-3(2*H*)-one (**45**, R = H) or its 2-methyl analog (**45**, R = Me). The synthesis of annelated imidazo[2,1-*b*]thiazoles (e.g., **46**) can be achieved in one step by reaction of 2,3-dichloroquinoxaline with **43**. The intramolecular cyclization of 1-vinylimidazole-2-thiones to 2,5-dimethyl-3,6-arylimidazo[2,1-*b*]thiazoles with excellent yield has been reported (93T6619).



## 2. From 2-Aminothiazoles

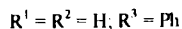
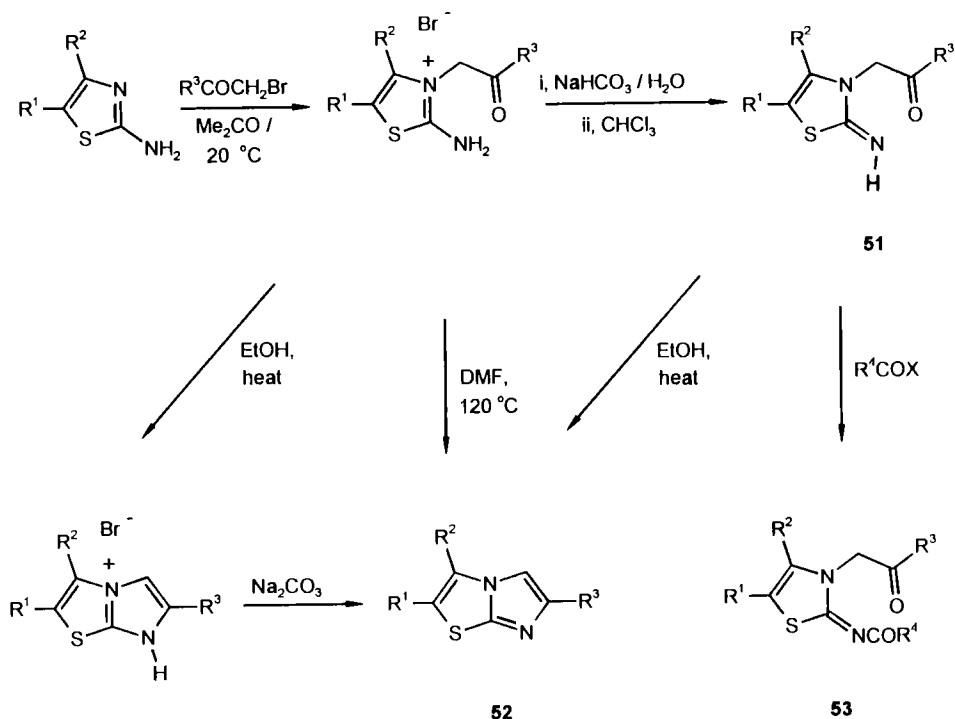
The most important and common method for the synthesis of imidazo[2,1-*b*]thiazoles [86HC(46)77] is the cyclocondensation of 2-aminothiazoles with  $\alpha$ -halo ketones (37YZ308; 55CB1109; 71JPR977; 72YZ51); thiazolium salts of type **47** (Scheme 2) are intermediates. For many years it remained unclear



SCHEME 2

whether the first reaction step involves attack at the endo- or exo-nitrogen atom of the 2-aminothiazoles. As shown in Scheme 2, two isomeric products (**49**, **50**) can result.

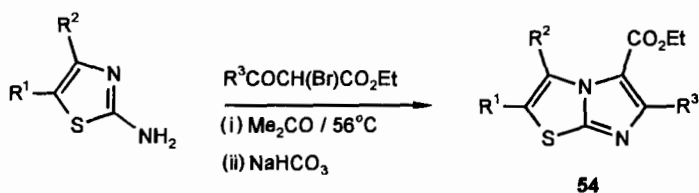
Although alkylation at N(3) was already assumed in previous studies (75MI1; 79JHC1201; 89JHC1875), Meakins *et al.* have shown definitely that it is the primary step in this reaction sequence irrespective of the electrophilic nature of the reactant and that *exo-N*-substituted products arise from subsequent isomerization [89JCS(P1)643; 91S621; 92JCS(P1)2029]. Efficient procedures have been developed for preparing a wide range of 2,3,6-substituted imidazo[2,1-*b*]thiazoles **52** [89JCS(P1)643]. In these cases *endo-N* attack with subsequent ring closure to **52** took place. Amides of type **53** are available from **51** by acylation [82JCS(P1)939].



$R_1$  to  $R_3$ : see Table II

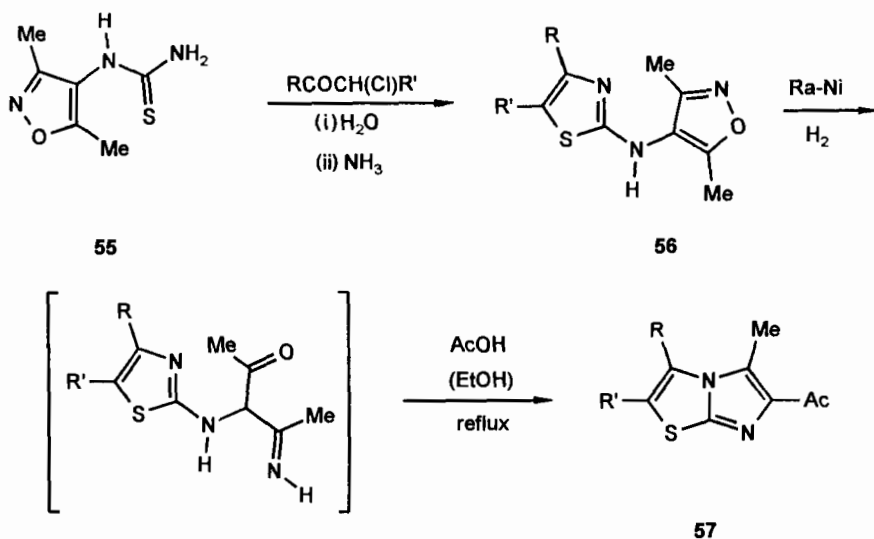
5-Alkoxy carbonyl imidazo[2,1-*b*]thiazoles **54** are accessible by reaction of 2-aminothiazoles with  $\alpha$ -halo  $\beta$ -ketoesters [92JCS(P1)2029].





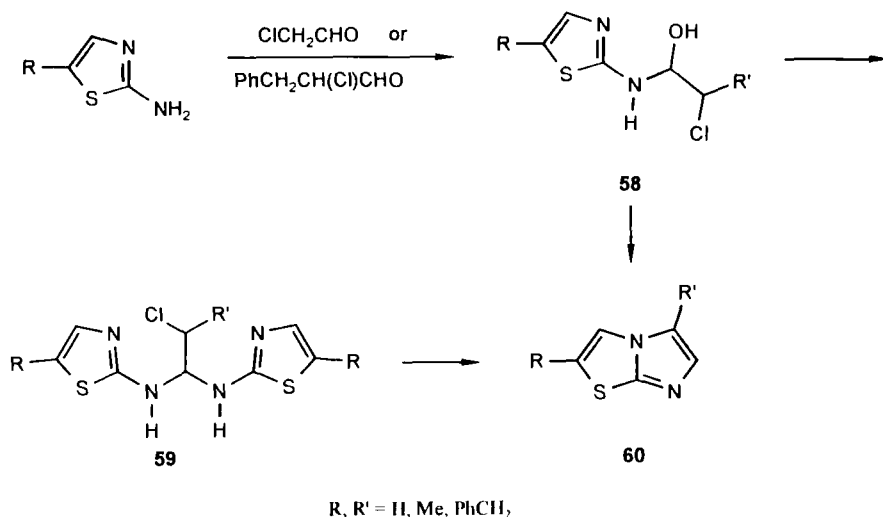
R<sub>1</sub> to R<sub>3</sub>: see Table II

Sprio *et al.* reported the preparation of 6-acetylimidazo[2,1-*b*]thiazoles derivatives **57** (74JHC91). The synthesis involves substituted 4-(2-thiazolyl)aminoisoxazoles **56**, which were obtained in good yield by the reaction of *N*-(3,5-dimethylisoxazol-4-yl) thiourea **55** with  $\alpha$ -chloro ketones. Subsequent isoxazole ring opening led to intermediates which readily underwent cyclization by refluxing in acetic acid or ethanol/hydrochloric acid.

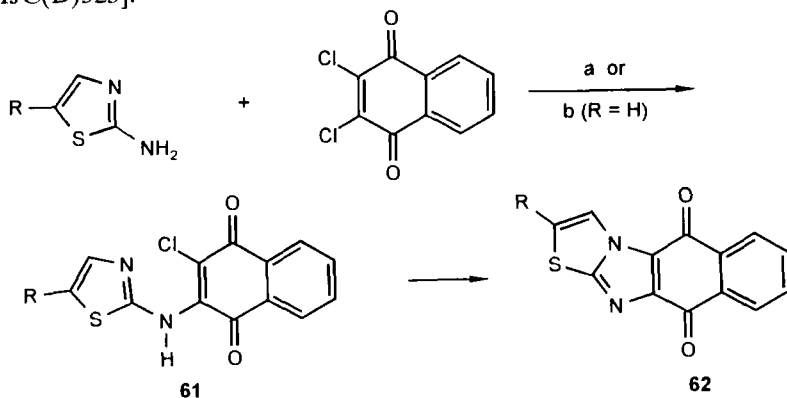


R, R' = Me, Ph

$\alpha$ -Halo aldehydes offer a route to various 2,5-disubstituted imidazo[2,1-*b*]thiazoles [93JCR(M)1218, 93JCR(S)201]. The amins **58** cyclize either in one step (**58**, R = Me, R' = H) or stepwise through bis(aminothiazoles) **59** leading to **60**.



Condensed derivatives have also been prepared. Reaction of 2-aminothiazoles with 2,3-dichloro-1,4-naphthoquinone yields naphth[2,3-*b*]imidazo[2,1-*b*]thiazole-5,10-dienones **62** via thiazolylaminoquinones **61**. Cyclization can be effected either with diethylaniline (method a) [77IJC(B)356] or with sodium hydroxide and tetrabutylammonium bromide (TBAB) catalyst (method b) (82H333). Following route b, compound **62** (R = Et) can be isolated in 92% yield. Reactions between 2-aminothiazoles and chloranil leading to dithiazolobenzobisimidazolidiones have also been reported [79IJC(B)523].



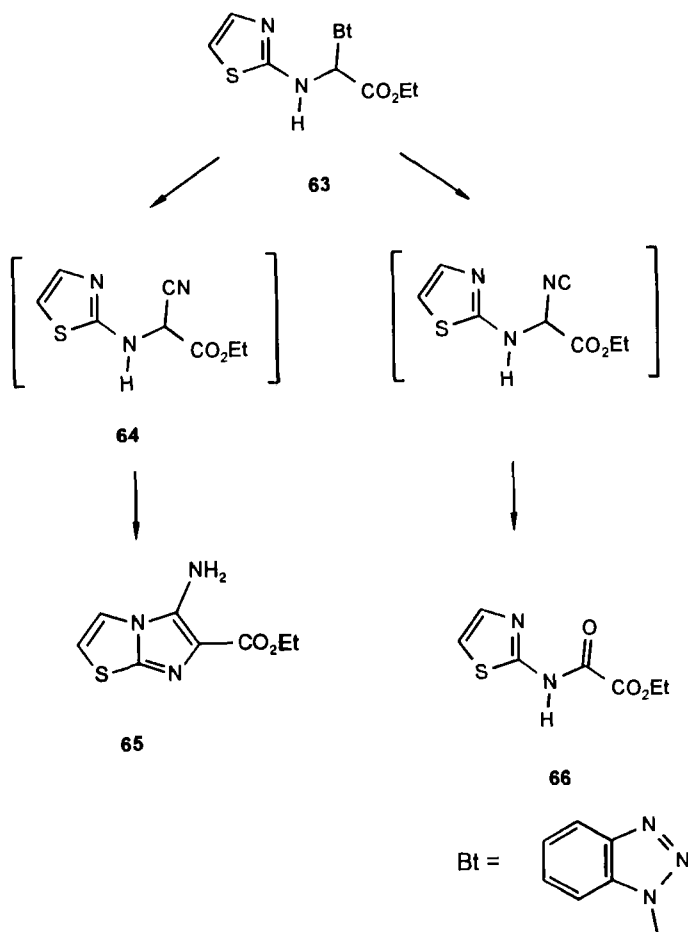
R = H, Me, Et

a = PhN(Et)<sub>2</sub> / EtOH

b = 50% aq. NaOH / benzene / TBAB

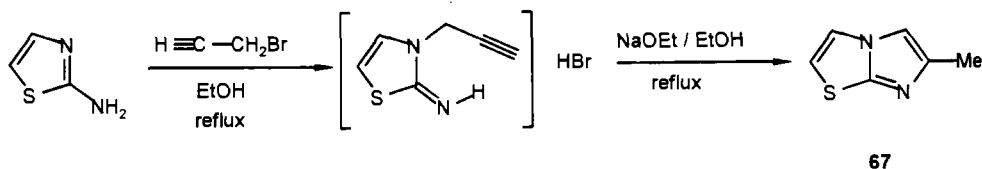
A benzotriazole-assisted synthesis of ethyl 5-aminoimidazo[2,1-*b*]thiazole-6-carboxylate **65** has been developed (96TL1787). Traces of compound **63** were isolated from 2-aminothiazole **23** using benzotriazole and freshly distilled ethyl glyoxylate in benzene, whereas by application of  $\alpha$ -benzotriazolyl- $\alpha$ -morpholino acetate with methyl iodide in THF, **63** was isolated in 40% yield. Subsequent treatment of **63** with potassium cyanide in ethanol at rt involves substitution of the benzotriazole moiety. Intramolecular cyclization of **64** yields **65**, albeit in 10% yield.  $\alpha$ -Ketoester **66** is also obtained (Scheme 3).

A less convenient route to 6-methylimidazo[2,1-*b*]thiazole makes use of prop-2-ynyl bromide and 2-aminothiazole (65BEP660274; 69JPP69/32793).



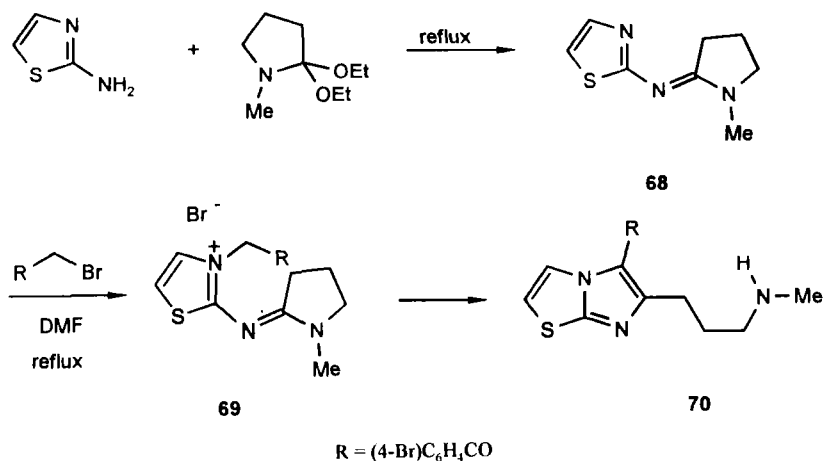
SCHEME 3

Cyclization of the intermediate imine with sodium ethylate in ethanol leads to **67** (65BEP660274); a direct approach (69JPP69/32793) has subsequently been achieved by refluxing 2-aminothiazole with prop-2-ynyl bromide in butanol.

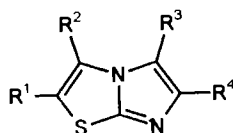


As reported by Liebscher and co-workers (93S521) lactamimino heterocycles (**68**) are accessible by reaction of 2-aminothiazole with lactam acetals (e.g., 2,2-diethoxy-1-methylpyrrolidine). They can be transformed into *N*-alkylated salts by reaction with CH-acidic phenacyl halides. In almost all cases, these salts cannot be cyclized to the corresponding imidazo[2,1-*b*]thiazoles even when strong bases and prolonged heating are applied. Only in one case [**69**, R = (4-Br)C<sub>6</sub>H<sub>4</sub>CO] the 5-(4-bromobenzoyl)-6-[3-(methylamino)propyl]imidazo[[2,1-*b*]thiazole<sup>3</sup> **70** could be isolated (66%). Probably the success of the cyclization depends on the nature of the electron-withdrawing substituent R and on the ring size of the lactam imine ring. In addition, formation of *exo-N* alkylation products is possible.

In Table II some imidazo[2,1-*b*]thiazoles are compiled. These have been prepared by methods outlined in the previous sections.



<sup>3</sup> In the original article (93S521), this was denoted as 3-(4-bromobenzoyl)-2-[3-(methylamino)propyl] imidazo[2,1-*b*]thiazole.

TABLE II  
 IMIDAZO[2,1-*b*]THIAZOLES


R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	Method of preparation	Ref.
H	H	H	H	A <sup>a</sup>	73JCS(P2)1926; 93JCR(M)1218
				B <sup>b</sup>	66MI1
				C <sup>c</sup>	67MI2; 70KGS508
H	H	H	Me	A	72YZ51; 73JCS(P2)1926; 89JCS(P1)643; 92JCS(P1)2029
H	H	H	CF <sub>3</sub>	A	86JHC1031
H	H	H	Aryl	A	55CB1109; 56ZOB2905; 61LA145; 66BSF1277; 67G488; 69JPP69/ 32793; 72YZ51; 73JCS(P2)1926; 74USP3804823; 86MI1; 88JHC129; 89JCS(P1)643; 92JCS(P1)2029
H	H	H	Hetaryl	A	68KGS178; 71JPR977; 81M1387
H	H	Ph	H	A	93JCR(M)1218
H	H	Aryl	Aryl	B	67CJC2903 <sup>d</sup>
H	H	Ph	Ph	A	61LA145
				B	70KGS508
H	Me	H	Me	A	89JCS(P1)643
H	Me	H	Aryl	A	61LA153; 67G1286; 69JPP69/32793; 72YZ51; 56ZOB458
				B	70KGS508; 70KGS512
H	Me	H	H	B	70KGS512
H	Ph	H	H	B	70KGS512
H	Aryl	Aryl	Aryl	B	88JJC(B)570
Aryl	H	Ph	H	A	93JCR(M)1218
Me	H	CO <sub>2</sub> Et	Me	A	36CB1650; 92JCS(P1)2029
Me	H	Ph	Ph	A	61LA145
				B	70KGS508
CO <sub>2</sub> Et	Me	H	Aryl	A	51YZ756; 80BCJ3308
Ac	Me	H	H	B	70KGS512
Me	Me	H	Hetaryl	A	71JPR977
Me	Me	Ph	Ph	A	61LA145
Ph	Ph	Ph	Ph	A	61LA145

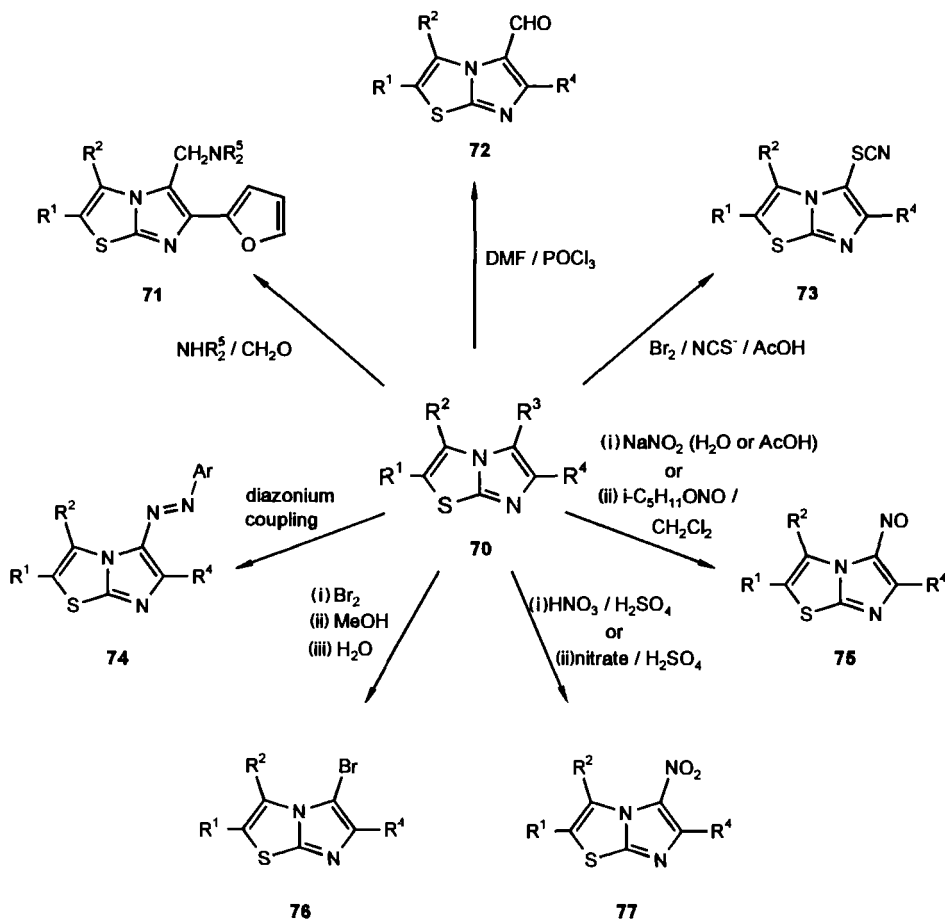
<sup>a</sup> From 2-aminothiazoles.<sup>b</sup> From 2-mercaptoimidazoles.<sup>c</sup> From imidazo[2,1-*b*]thiazole-5-carboxylic acid.<sup>d</sup> See also <92JCS(P1)707; 92MI2; 96JCR(M)116; 96JCR(S)4>.

## B. REACTIONS

1. *Reactions at Ring Atoms*

a. *Reactions with Electrophiles.* Imidazo[2,1-*b*]thiazoles undergo electrophilic substitution reactions at position 5, such as bromination (61LA145; 72KGS1353, 72YZ51), nitration (61LA153; 69JMC1031; 79ZOR2547; 91H2083), nitrosation (61LA145; 62LA108; 72KGS1353), thiocyanation [68JPP68/24187; 72YZ51; 91JCS(P1)855], formylation (69JMC1031; 79MI1; 82AP451; 87MI1; 88MI1), aminomethylation [69JMC1031; 75KGS(9)1208], and diazonium coupling (62LA108; 67G488; 71BRP1236656; 75USP3928311) (Scheme 4).

Arguments based on  $^1\text{H}$  NMR have been proposed for these results [73JCS(P2)1926]. Beyer and coworkers (61LA145) investigated the reaction of 6-phenylimidazo[2,1-*b*]thiazoles (**70**,  $\text{R}^4 = \text{Ph}$ ) with an excess of bromine. Perbromides could be isolated as stable products; after treatment with methanol and water monobrominated compounds were obtained in good yield. No bromination of the phenyl ring was observed. Attempts to obtain a 2-bromoimidazo[2,1-*b*]thiazole via bromination of 5-methyl or 3-methyl-6-phenylimidazo[2,1-*b*]thiazole with an excess of bromine in acetic acid failed. In the following years a variety of 5-bromo-6-aryl- and -alkylimidazo[2,1-*b*]thiazoles have been prepared [91CCC2430, 91JCS(P1)855]. The course of the bromination reaction of 6-(2'-furyl)imidazo[2,1-*b*]thiazoles has been investigated in detail by Saldabol *et al.* [72KGS1353; 75KGS(11)55; 78KGS258; 79ZOR2547]. In the presence of 1 mol bromine, monobromination takes place either at C(5) or in the side chain. With an excess of bromine, dibromo derivatives are obtained. Interestingly, on treatment of **76** ( $\text{R}^1 = \text{R}^2 = \text{H}$ ,  $\text{R}^4 = 2\text{-furyl}$ ) in DMF, partial debromination to **70** ( $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$ ,  $\text{R}^4 = 2\text{-furyl}$ ) with subsequent bromination of the furyl substituent is observed (77ZOR2626). Chlorination at position 5 has also been achieved (91CCC2430). Nitration (61LA153) and nitrosation (61LA145; 62LA108) of imidazo[2,1-*b*]thiazoles has also been studied by Beyer and co-workers. Treatment of 6-phenylimidazo[2,1-*b*]thiazole nitrate (**70**,  $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$ ,  $\text{R}^4 = \text{Ph}$ .) with conc. sulfuric acid leads to the corresponding 6-*p*-nitrophenyl substituted compound [**70**,  $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$ ,  $\text{R}^4 = (4\text{-NO}_2)\text{C}_6\text{H}_4$ ]. Reaction of 6-phenylimidazo[2,1-*b*]thiazole (**70**,  $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$ ,  $\text{R}^4 = \text{Ph}$ ) with nitrating acid affords the dinitro compound [**77**,  $\text{R}^1 = \text{R}^2 = \text{H}$ ,  $\text{R}^4 = (4\text{-NO}_2)\text{C}_6\text{H}_4$ ]. Nitration at position 5 can easily be achieved if the *para*-position of the phenyl ring is substituted. If C(5) and the *para*-position of the side chain are substituted, nitration may occur at C(2). For further examples of 5-nitro substituted imidazo[2,1-*b*]thiazoles see Paolini and Lendvay (69JMC1031), Saldabol *et al.* (79ZOR2547); and Vanelle *et al.* (91H2083). 6-Phenylimidazo[2,1-*b*]thia-



$\text{R}^1, \text{R}^2, \text{R}^3, \text{R}^4 = \text{H, alkyl, aryl, hetaryl}$

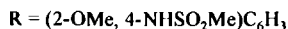
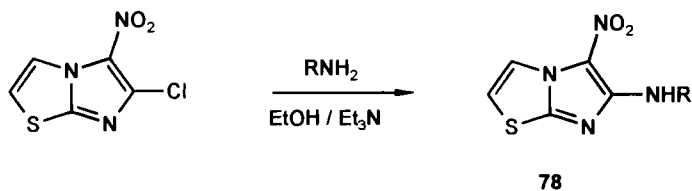
$\text{R}_2^5\text{N} = \text{piperidino, pyrrolidino, morpholino}$

SCHEME 4

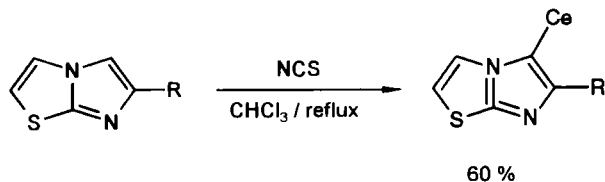
zoles can be converted into the corresponding 5-nitroso compounds **75**. Attempts to prepare 6-*t*-butyl-5-nitroso substituted compounds (**75**,  $\text{R}^1 = \text{R}^2 = \text{H}$ ,  $\text{R}^4 = t\text{Bu}$ ) [91JCS(P1)855] with sodium nitrite in acetic acid failed, but this substitution could be achieved with isoamyl nitrite. 6-*t*-Butylimidazo[2,1-*b*]thiazole undergoes thiocyanation at position 5 on treatment with bromine and  $\text{NH}_4\text{SCN}$  in acetic acid [91JCS(P1)855]. Similarly, 6-chloro-5-thiocyanatoimidazo[2,1-*b*]thiazole has been prepared (69JMC1031) according to the procedure of Takatori and Nishida

(51YZ1367). On treatment of 6-*p*-chlorophenyl-3-methyl-5-nitroso-imidazo[2,1-*b*]thiazole with dilute hydrochloric acid in dioxane at rt a ring transformation occurs [92JCS(CC)1394]. Vilsmeier-Haack reaction of 3-methyl-6-phenylimidazo[2,1-*b*]thiazole (**70**,  $R^1 = R^3 = H$ ,  $R^2 = Me$ ,  $R^4 = Ph$ ) at C(5) to **72** was realized by reaction with DMF and  $POCl_3$  in chloroform [87MI2]. Further examples have been reported [69JMC1031; 82AP451; 88MI1; 91JCS(P1)855; 92MI1]. Secondary amines together with formaldehyde/acetic acid were used to prepare a variety of Mannich bases **71** [75KGS(9)1208]. Using equimolar amounts of aminomethylating agents a substitution occurs primarily at position 5 of the imidazo[2,1-*b*]thiazole system; an excess of aminomethylating agents leads to bis(aminomethyl) derivatives substituted both at C(5) and the side chain. Diazonium coupling of 6-phenylimidazo[2,1-*b*]thiazole (**70**,  $R^1 = R^2 = R^3 = H$ ,  $R^4 = Ph$ ) at C(5) with *o*-nitrodiazoniumbenzene chloride leads to **74** [ $R^1 = R^2 = H$ ,  $R^4 = Ph$ ,  $Ar = (2-NO_2)C_6H_4$ ] (62LA108). 5-Substituted compounds showed no reactivity.

b. *Reactions with Nucleophiles.* Only a few nucleophilic substitution reactions have been carried out. 6-Chloro-5-nitroimidazo[2,1-*b*]thiazole undergoes nucleophilic substitution with 4-aminomethane sulfonamide to give **78** (93MI4).



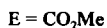
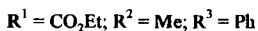
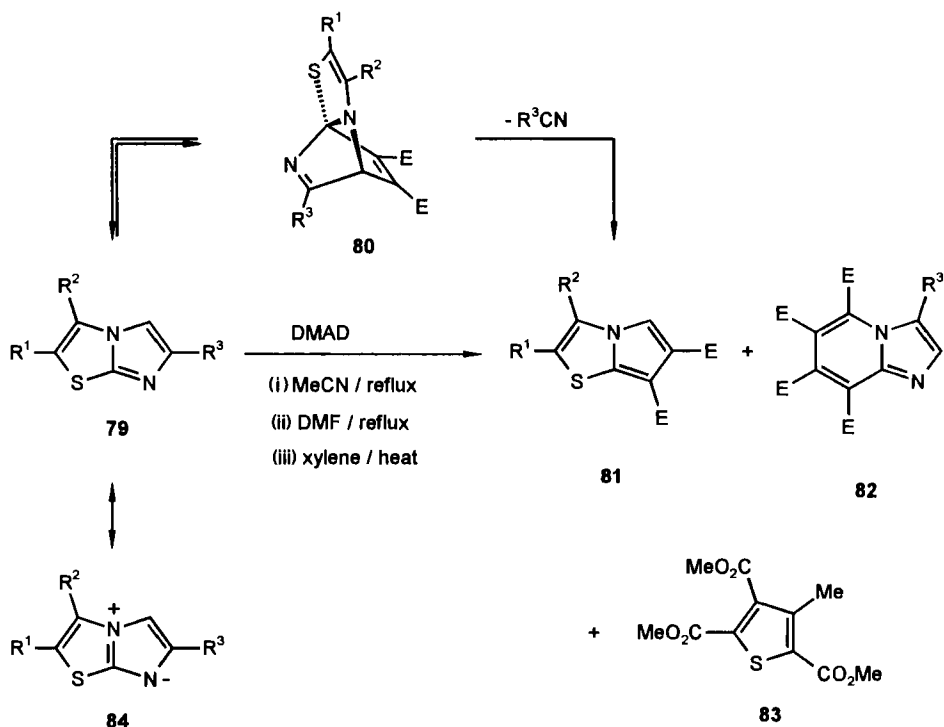
c. *Reactions with Radicals.* Imidazo[2,1-*b*]thiazoles react with NBS and NCS leading to 5-bromo and 5-chloro derivatives, respectively (69JMC1031; 72USP3632816; 91CCC2430). 5-Chloro-6-phenylimidazo[2,1-*b*]thiazole can be obtained in 60% yield from 6-phenylimidazo[2,1-*b*]thiazole in the presence of NCS.



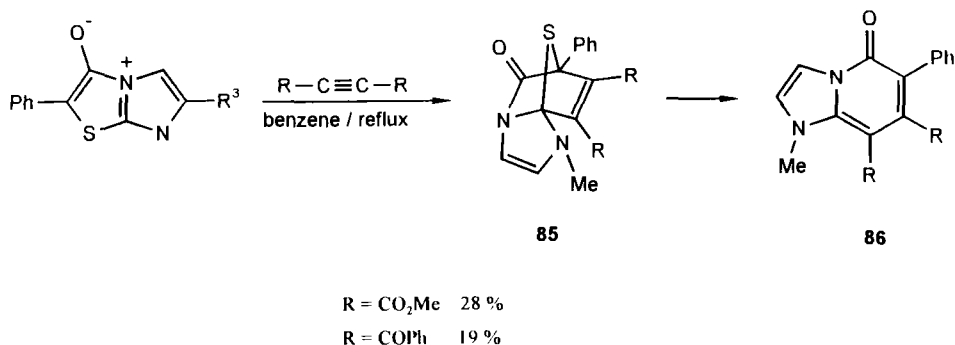


d. *Cycloadditions.* Imidazo[2,1-*b*]thiazoles undergo cycloadditions with reactive acetylenic esters (80BCJ3308). The course of the reaction between ethyl 3-methyl-6-phenylimidazo[2,1-*b*]thiazole-2-carboxylate and DMAD depends on the solvent. When the reaction was carried out in boiling acetonitrile three products (**81**, **82**, **83**) were isolated in 24, 42, and 41% yield, respectively.

With hot xylene as solvent, compound **81** was obtained as the sole product. In this latter case the reaction proceeds via a Diels–Alder addition of **79** with DMAD followed by elimination of a nitrile ( $R^3CN$ ). In aprotic polar solvents an imidazo[1,2-*a*]pyridine (**82**) is formed. This reaction can be considered to be a 1,3-dipolar cycladdition of **84** with 2 mol DMAD via a 1,4-dipolar intermediate.

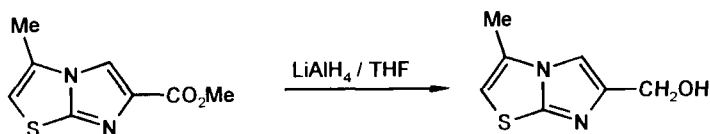
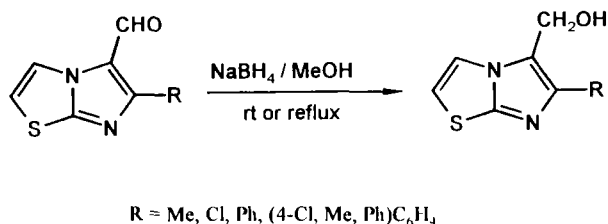


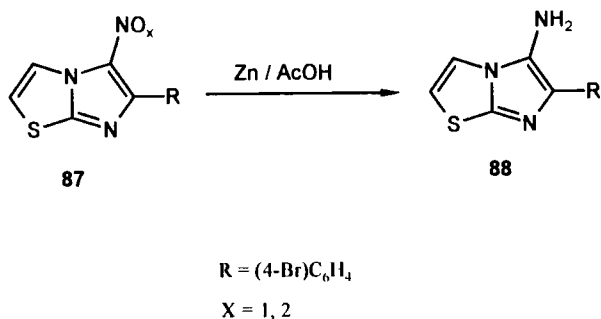
Reactions of imidazo[2,1-*b*]benzothiazoles and imidazo [2,1-*b*]thiazoles with dibenzoylacetylene (82BCJ200) proceed similarly. Potts and Kanemasa (79JOC3803) found that DMAD and dibenzoylacetylene react with anhydro-3-hydroxy-7-methyl-2-phenylimidazo[2,1-*b*]thiazolium hydroxide to give **86**, although in poor yield. Probably adducts of type **85** are intermediates.



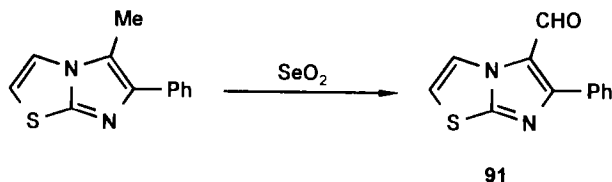
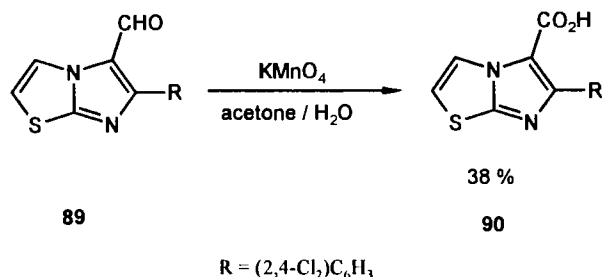
## 2. Side-Chain Reactions

a. *Reduction Reactions.* 5-Hydroxymethyl substituted imidazo[2,1-*b*]thiazoles are obtained in good yield by reduction of the corresponding 5-formyl compounds with  $NaBH_4$  in methanol (80FES896; 82AP451). With  $LiAlH_4$  methyl 3-methylimidazo[2,1-*b*]thiazole-6-carboxylate can easily be transformed into the corresponding 6-hydroxymethyl compound (75GEP2505068). Reduction of 5-nitro- or 5-nitroso-imidazo[2,1-*b*]thiazoles **87** with zinc in acetic acid leads to 5-amino compounds **88** (62LA113).



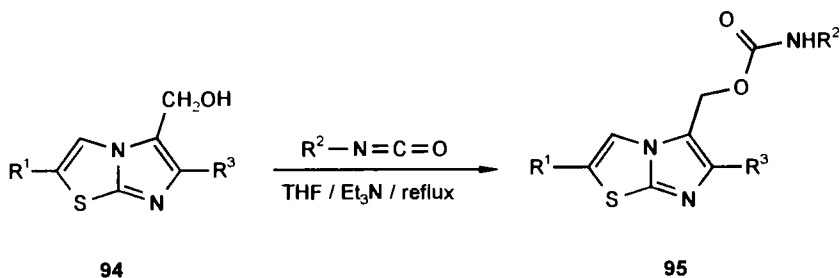
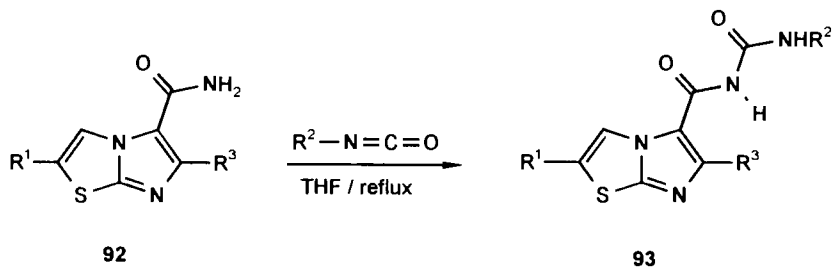


b. *Oxidation Reactions.* The imidazo[2,1-*b*]thiazole system is stable toward strong oxidizing agents (80MI1; 88MI1). 6-Arylimidazo[2,1-*b*]thiazole-5-carboxylic acid **90** is available with 38% yield from **89** using potassium permanganate in aqueous acetone at ambient temperature. 5-Methyl-6-phenylimidazo[2,1-*b*]thiazole can be oxidized with  $\text{SeO}_2$  to the corresponding 5-formyl compound (79MI1). Attempts to synthesize 6-formyl compounds via  $\text{SeO}_2$  oxidation failed (79MI1); 5,5'-bis(6-methylimidazo[2,1-*b*]thiazolyl)selenide was formed.

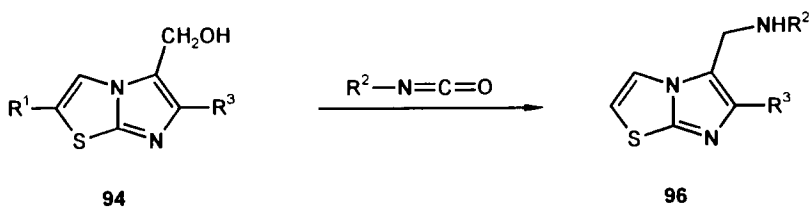


c. *Miscellaneous Transformations.* Reaction of imidazo[2,1-*b*]thiazole-5-carboxy amides **92** and 5-hydroxymethylimidazo[2,1-*b*]thiazoles **94** with isocyanates leads to acylureas **93** and carbamates **95** (80FES896; 88MI1; 89JHC525). Saponification of **95** ( $\text{R}^1 = \text{H}$ ,  $\text{R}^2 = \text{R}^3 = \text{aryl}$  [(4-Cl) $\text{C}_6\text{H}_4$ ],

THF/H<sub>2</sub>O/reflux] yields 5-aminoaryl substituted imidazo[2,1-*b*]thiazoles **96**. These compounds have also been obtained directly by treatment of **94** ( $R^1 = \text{H}$ ,  $R^3 = \text{Me}$ ) with isocyanates.



$R^1 = \text{H}, \text{Me}; R^2 = \text{alkyl, aryl}; R^3 = \text{Me, Cl, aryl}$



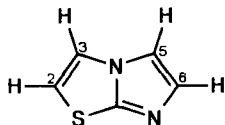
$R^1 = \text{H}; R^2 = (4\text{-Cl})\text{C}_6\text{H}_4; R^3 = \text{Me}, (4\text{-Cl})\text{C}_6\text{H}_4$

The acylation of 5-hydroxymethylimidazo[2,1-*b*]thiazoles **96** (with, e.g.,  $R^1 = \text{H}$ ,  $R^3 = \text{Ph}$ ) has been reported (80FES896). In line with expectations, ethyl esters of imidazol[2,1-*b*]thiazole carboxylic acids on basic hydrolysis

afford the free acids (75GEP2505068; 77FES735; 83FES533; 89JHC1875; 95MI2). Reaction of ethyl imidazo[2,1-*b*]thiazole 6-carboxylate with hydrazine hydrate leads to a hydrazide (88MI1); with ammonia an amide is obtained (79FES417). Amides are also available by treating 6-carboxylic acids with thionyl chloride and ammonium hydroxide (82MI1). Formation of amide oximes can be achieved by reaction of imidazo[2,1-*b*]thiazole-5-carbonitriles with hydroxylamine in refluxing ethanol (88MI1). Transformations of formyl-substituted compounds into derivatives are well known. 5-Formyl-6-*p*-chlorophenylimidazo[2,1-*b*]thiazole reacts with aminoguanidine hydrochloride in ethanol to the corresponding guanylhyazone (92JMC4634). 6-Formylimidazo[2,1-*b*]thiazole can be converted into a thiosemicarbazone (88MI1). Nucleophilic esterification of 6-chloroimidazo[2,1-*b*]thiazole-5-carboxylic acid with allyl bromide, propargyl bromide, and chloroacetonitrile (THF/Et<sub>3</sub>N/reflux) has been reported (93AP141). Decarboxylation of imidazo[2,1-*b*]thiazole carboxylic acids is not widely used, although some examples are known [67MI2; 70KGS508; 92JCS(P1)2029]. 6-Methylimidazo[2,1-*b*]thiazole-5-carboxylic acid was obtained by alkaline hydrolysis of the corresponding ethyl ester. Subsequent decarboxylation was achieved by heating with hydrochloric acid [92JCS(P1)2029].

### C. SPECTROSCOPIC DATA AND STRUCTURAL PROPERTIES

The <sup>1</sup>H NMR spectrum of the parent compound has been reported [93JCR(M)1218, 93JCR(S)201].



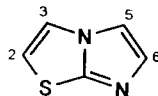
<sup>1</sup>H NMR (CDCl<sub>3</sub>) (values in ppm):  $\delta(\text{H-2}) = 6.72$ ,  $\delta(\text{H-3}) = 7.33$ ,  $\delta(\text{H-5}) = 7.36$ ,  $\delta(\text{H-6}) = 7.23$ ;  $J_{2,3} = 4.49\text{ Hz}$ ,  $J_{2,6} = 1.21\text{ Hz}$ ,  $J_{5,6} = 1.35\text{ Hz}$ .

For a previous study see Taddei *et al.* [73JCS(P2)1926]. As in a number of other cases [63ACSA280; 64AJC1128; 65BCJ508, 65JCS4368, 65TL2393; 68JOC1355; 84CHEC(4)973] a W (zigzag) coupling is observed between H-2 and H-6.

Spectral data of some representative examples are given in Table III. Table IV contains <sup>13</sup>C NMR data. In addition, <sup>15</sup>N and <sup>14</sup>N spectra of imidazo[2,1-*b*]thiazole have been reported (89MI2).

Infrared absorption spectra have frequently been used in structure proof of imidazo[2,1-*b*]thiazoles, but identification of functional groups is the

TABLE III  
<sup>1</sup>H NMR DATA OF IMIDAZO[2,1-*b*]THIAZOLES

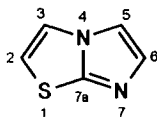


Position/Substituent				$J_{2,3}$ (Hz)	$J_{2,6}$ (Hz)	$J_{5,6}$ (Hz)	Other couplings (Hz)	Ref.
2	3	5	6					
6.74 H	7.21 H	2.34 Me	6.97 H	4.49	1.10		$J_{\text{CH3,6-H}}$ 1.06	73JCS(P2)1926
6.64 H	7.22 H	7.12 H	2.31 Me	4.43			$J_{\text{CH3,5-H}}$ 1.00	73JCS(P2)1926
6.65 H	7.24 H	7.60 H	— Ph	4.50				73JCS(P2)1926
6.68 H	7.32 H	7.15 H	2.71 Et	4.41			$J_{\text{CH2,5-H}}$ 0.93	73JCS(P2)1926
2.33 Me	7.00 H	7.46 H	— Ph				$J_{\text{CH3,3-H}}$ 1.41	73JCS(P2)1926
7.00 H	8.23 H	— CO <sub>2</sub> Et	— Ph	5.1				92JCS(P1)2029
6.53 H	2.66 Me	— CO <sub>2</sub> Et	— Ph					92JCS(P1)2029
6.88 ud <sup>a</sup> H	7.39 ud <sup>a</sup> H	7.39 s <sup>b</sup> H	— Cl	4.5				69JMC1031
— Et	7.15 H	7.63 H	— Ph				$J_{\text{CH2,3-H}}$ 1.3	89JCS(P1)643
— Et	7.04 H	7.06 H	— Me				$J_{\text{CH2,3-H}}$ 1.3 $J_{\text{CH3,5-H}}$ ~0.9	89JCS(P1)643
7.12 H	7.79 H	7.87 H	— 2-furyl	4.4				72KGS1353

<sup>a</sup> Unsymmetrical doublet.

<sup>b</sup> Singlet.

TABLE IV  
<sup>13</sup>C NMR DATA OF IMIDAZO[2,1-*b*]THIAZOLES



Position/substituent					
2	3	5	6	7a	Ref.
110.08	124.21	111.01	134.59	149.20	95MI2
H	CH <sub>2</sub> CO <sub>2</sub> Et	H	H		
109.76	124.27	106.59	147.65	149.47	95MI2
H	CH <sub>2</sub> CO <sub>2</sub> Et	H	Ph		
110.25	118.04	111.28	140.01	148.38	95MI2
H	H	H	CH <sub>2</sub> CO <sub>2</sub> Et		
110.77	132.32	116.62	138.79	150.25	95MI2
H	Ph	H	CO <sub>2</sub> H		
110.11	132.55	107.80	140.96	149.17	95MI2
H	Ph	H	CH <sub>2</sub> CO <sub>2</sub> Et		
110.95	131.59	116.19	138.95	150.33	95MI2
H	(4-Cl)C <sub>6</sub> H <sub>4</sub>	H	CO <sub>2</sub> H		
110.09	131.40	109.03	131.40	148.89	95MI2
H	(4-Cl)C <sub>6</sub> H <sub>4</sub>	H	CH <sub>2</sub> CO <sub>2</sub> Et		
113.29	121.49	114.44	153.76 <sup>a</sup>	152.60 <sup>a</sup>	95MI2
H	H	CO <sub>2</sub> Et	Ph		
132.20	139.62	131.60	140.00	140.81	93MI5
H	CH <sub>2</sub> CON(Me) <sub>2</sub>	H	Ph		
132.22	139.32	131.72	140.90	141.62	93MI5
H	CH <sub>2</sub> CON(Et) <sub>2</sub>	H	Ph		
121.38	129.18	119.07	142.71	146.16	93T6619
Me	Ph	Me	Ph		
129.23	127.71	125.57	142.22	146.3	93T6619
Et	Ph	Et	Ph		

<sup>a</sup> Assignment uncertain.

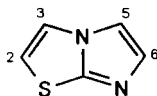
most important application. Assignments of the bands belonging to the heterocyclic system are very rare [88IJC(B)570; 93MI5].

A mass spectral fragmentation scheme for the unsubstituted imidazo[2,1-*b*]thiazole system has been published (74KGS935).

UV data for the parent compound are still lacking. Table V gives UV data for some 6-acyl substituted imidazo[2,1-*b*]thiazoles.

X-ray structure determinations were performed for 6-phenylimidazo[2,1-*b*]thiazole (72CSC345), ethyl 3-phenyl-6-*p*-chlorophenylimidazo[2,1-*b*]thia-

TABLE V  
UV DATA OF IMIDAZO[2,1-*b*]THIAZOLES



Position/substituent				$\lambda_{\max}$	$\lg \epsilon$	Ref.
2	3	5	6			
H	H	Me	Ac	245	4.63	74JHC91
H	Me	Me	Ac	245	4.99	74JHC91
Me	Me	Me	Ac	246, 268 (sh)	4.03, 3.99	74JHC91
-(CH <sub>2</sub> ) <sub>4</sub> -		Me	Ac	248, 272 (sh)	4.00, 3.92	74JHC91
-(CH <sub>2</sub> ) <sub>5</sub> -		Me	Ac	246, 262 (sh)	4.07, 3.85	74JHC91

zole-2-carboxylate [87AC(C)2415], and 3-phenyl-6-*p*-fluorophenylimidazo[2,1-*b*]thiazole-2-acetic acid (89MI1). Bond lengths are listed in Table VI.

Computational studies in the field of imidazo[2,1-*b*]thiazoles are still lacking. The results of some semiempirical (AM1, PM3) (90MI1), *ab initio* (93MI1), and density functional theoretical (95MI1) investigations (96UP2) are also given in Table VI.

#### D. APPLICATIONS AND BIOLOGICAL PROPERTIES

Biological activities of imidazo[2,1-*b*]thiazoles have been examined by many authors. Table VII summarizes results.

Imidazo[2,1-*b*]thiazoles are also used as azo dyestuffs (66MI2; 71BRP1236656; 74USP3804823; 75USP3928311).

### VII. Imidazo[2,1-*b*][1,3,4]thiadiazoles

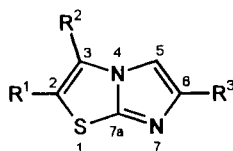
#### A. SYNTHESIS

##### 1. From 1,3,4-Thiadiazoles

The most common methods for the synthesis of imidazo azines and imidazo azoles are the condensation of heterocyclic amines with  $\alpha$ -halo



TABLE VI

**97**a:  $R^1 = R^2 = R^3 = H$ b:  $R^1 = R^2 = H$ ;  $R^3 = Ph$ c:  $R^1 = EtO_2CH_2$ ,  $R^2 = Ph$ ,  $R^3 = (4-Cl)C_6H_4$ BOND DISTANCES OF **97a,b,c** (AM1, PM3, AB INITIO, DFT, EXP.) (VALUES IN Å) <96UP2>

Method	$r_{12}$	$r_{1,7a}$	$r_{23}$	$r_{34}$	$r_{45}$	$r_{4,7a}$	$r_{56}$	$r_{67}$	$r_{7,7a}$
AM1 <sup>b</sup>	1.702	1.699	1.372	1.391	1.385	1.443	1.422	1.407	1.348
PM3 <sup>b</sup>	1.756	1.743	1.359	1.418	1.396	1.427	1.396	1.408	1.343
6-31G <sup>*a</sup>	1.762	1.747	1.328	1.388	1.380	1.354	1.353	1.374	1.288
6-31G <sup>*b</sup>	1.762	1.746	1.328	1.387	1.379	1.352	1.360	1.380	1.285
6-311G <sup>**a</sup>	1.762	1.744	1.327	1.388	1.381	1.352	1.353	1.374	1.286
6-311G <sup>**b</sup>	1.762	1.743	1.327	1.387	1.380	1.350	1.350	1.379	1.284
MP2/6-31G <sup>*a</sup>	1.745	1.741	1.358	1.389	1.380	1.384	1.384	1.379	1.324
DFT <sup>a,c</sup>	1.765	1.757	1.351	1.390	1.386	1.383	1.377	1.382	1.311
DFT <sup>a,d</sup>	1.764	1.754	1.348	1.389	1.386	1.381	1.375	1.380	1.307
DFT <sup>b,c</sup>	1.766	1.756	1.351	1.389	1.383	1.382	1.386	1.391	1.307
DFT <sup>b,d</sup>	1.764	1.753	1.348	1.389	1.384	1.380	1.384	1.388	1.304
Exp. <sup>b,e</sup>	1.735	1.725	1.344	1.420	1.382	1.389	1.389	1.413	1.311
Exp. <sup>f,g</sup>	1.766	1.747	1.362	1.381	1.374	1.369	1.374	1.397	1.301

<sup>a</sup> **97a.**<sup>b</sup> **97b.**<sup>c</sup> Becke3LYP/6-31G\*.<sup>d</sup> Becke3LYP/6-311G\*\*.<sup>e</sup> 72CSC345.<sup>f</sup> **97c.**<sup>g</sup> 87AX(C)2415.

carbonyl or related compounds. Using this methodology imidazo[2,1-*b*][1,3,4]thiadiazoles were prepared for the first time by Matsukawa and Ban (52YZ610; 54YZ1044). On treatment of 2-amino-1,3,4-thiadiazoles with phenacyl bromides, an alkylation at N-3 takes place<sup>4</sup> [see also Sitte *et al.* (67ZC341; 75M1291), but see later discussion]. The resulting salts were transformed to the free base (aqueous ammonia) and subsequently cyclized to the imidazo[2,1-*b*][1,3,4]thiadiazoles (boiling water, catalytic amount of acid).

<sup>4</sup> The alkylation of 2-amino-1,3,4-thiadiazoles was reported already by Freund and Meinicke (1896CB2514). See also Goerdeler and Roth (63CB534).

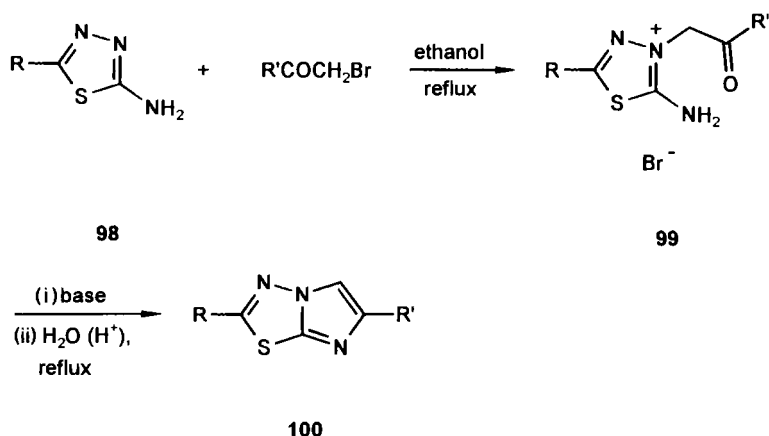


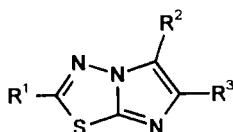
TABLE VII  
BIOLOGICAL PROPERTIES OF IMIDAZO[2,1-*b*]THIAZOLES

Biological function	Ref.
Antifungal and antibacterial	84IJC(B)798
Anti-inflammatory	81FES893; 82MI1; 83FES533; 92MI3; 93MI5
Anti-inflammatory and analgesic	79FES417; 95MI2
Antidiabetic	75GEP2505068
Antibacterial	65PHA629
Antimycobacterial	94MI3
Fungicidal	66PHA425
Positive inotropic activity	85MI2; 86MI2
Positive inotropic activity on isolated guinea pig atria	84MI2
Positive inotropic activity on spontaneously beating guinea pig atria	92MI1
Mitogenic activity on thymic lymphocytes	91MI3
Antitumor	80FES896
<i>In vitro</i> cytotoxicity on cultured HeLa cells	93MI4
Herbicidal	90EUP477808; 91CCC2430; 93MI6; 93MI7
Analgesic	81FES893
Ulcerogenic activity in rats	81FES893
Diuretic activity	87MI1; 92MI4
Anthelmintic activity	90FA953; 92FA63
Antipyretic activity	79FES417; 81FES893
Cardiotonic activity	86MI1
Antitubercular activity	77IJC(B)356

A great number of imidazothiadiazoles have been prepared using this methodology. Some results are given in Table VIII.

Further examples are given in several references [63LA113; 69GEP1804465; 71USP3615639; 74USP3809691; 75G777; 77BP1464259, 77CR(C)799; 78PS87; 85FES34; 86CCC2214; 90MI2, 90MI3; 91IJC(B)620, 91MI4; 92MI5; 93MI9, 93MI10, 93MIP1; 94IJC(B)686, 94JCR(S)38, 94MI4; 95PS11].

TABLE VIII  
IMIDAZO[2,1-*b*][1,3,4]THIADIAZOLES



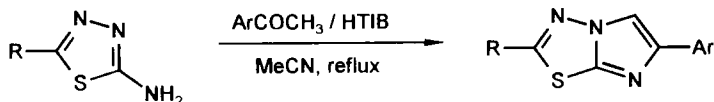
R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Ref.
H	H	Alkyl	54YZ658; 75G777
H, alkyl	H	Aryl <sup>a,b</sup>	52YZ610; 54YZ1044; 63LA113; 72YZ935; 74USP3804823; 75G777; 75USP3928311; 79GEP2823686; 86CCC2214
Alkyl	H	Aryl <sup>c</sup>	52YZ610; 54YZ1044; 67KFZ27; 72IJC598; 75G777; 79PHA144; 88JMC2221; 89JIC118; 90FA1341; 91IJC(B)620; 92FA63; 93H763; 94MI4
Alkyl	H	Alkyl	54YZ658; 72YZ935; 75G777; 83JHC1003
Aryl	H	Alkyl	54YZ658; 75G777
Aryl	H	Aryl	52YZ610; 65JHC287; 67KFZ27; 76FES41; 79GEP2823686; 82AP12; 84FES585; 89IJC(B)500; 89JIC118; 92MI6
Alkyl, aryl	Alkyl	Alkyl, aryl	75G777, 84FES585
H	Aryl	H	82JIC1170
Alkyl, aryl	Alkyl, aryl	H	79JIC716; 82JIC1170
H, alkyl, aryl	CH=O, carbalkoxy	H, alkyl, aryl	54YZ658; 69GEP1804465; 74USP3809691; 85FES190
H	Alkyl	Alkyl	75G777

<sup>a</sup> Aryl include phthalimidyl, hetaryl, naphthyl, etc.

<sup>b</sup> Different mp's have been reported for 6-(4'-nitrophenyl)imidazo[2,1-*b*][1,3,4]thiadiazole (273–4°C [52YZ610], 287°C [75G777]).

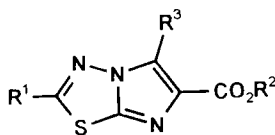
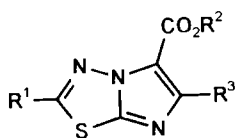
<sup>c</sup> Different mp's have been reported for 2-methyl-6-(4'-nitrophenyl)imidazo[2,1-*b*][1,3,4]thiadiazole (241–2°C [52YZ610], 255°C [75G777]).

The  $\alpha$ -halo ketone has also been prepared *in situ* (NBS, benzoyl peroxide, light) [89IJC(B)500]. Similarly, imidazo[2,1-*b*][1,3,4]thiadiazoles are accessible from 2-amino-1,3,4-thiadiazoles and acetophenones in the presence of hydroxy(tosyloxy)iodobenzene (HTIB). This latter method has been proposed as more convenient and versatile than the reaction of 2-amino-1,3,4-thiadiazoles with  $\alpha$ -halo ketones [94IJC(B)686, 94JCR(S)38, 94MI5].



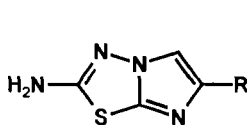
R = alkyl, aryl

For the preparation of **100** (or the corresponding salts) it is not necessary to isolate the free bases of **99** because cyclization can be effected in boiling water (or alcohols) or even with strong bases at rt (54YZ658). Generally speaking, when the condensation reaction between amine and halo ketone is performed at higher temperatures (e.g., DMF/reflux), the imidazo[2,1-*b*][1,3,4]thiadiazole is obtained directly (as salt). Derivatives with a free 5-position have lower thermal stability and condensation in DMF can lead to ring cleavage without formation of cyclic products. The presence of a methyl group at C-5 allows higher reaction temperatures (75G777). Disubstituted 5- (or 6-) carbalkoxy derivatives are obtained from 2-amino-1,3,4-thiadiazoles and alkyl 2-halogenoacetoacetic carboxylates (water/ethanol/reflux) (54YZ658) or with 3-bromo-2-oxopropionic acid esters (85FES190).



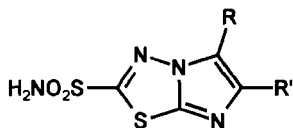
In contrast to imidazo[2,1-*b*][1,3,4]oxadiazoles (see Section III), imidazo[2,1-*b*][1,3,4]thiadiazoles form stable salts (hydrohalides, perchlorates, picrates, picronolates). Hydrohalides are often the primary products of the cyclization reaction.

2-Amino and 2-aminosulfonyl derivatives are prepared from the corresponding 1,3,4-thiadiazoles. In the former case the *N*(3)-alkylation products are isolated as intermediates.



R = alkyl, aryl

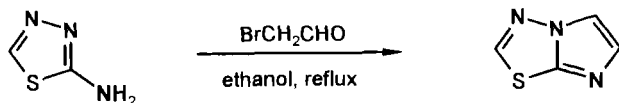
(77M665)



R = H, Me, Ph; R' = H, alkyl, aryl

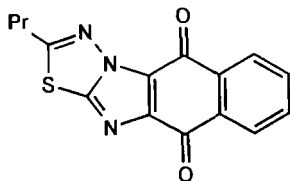
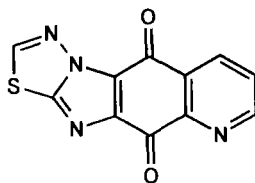
(80JMC117)

The parent compound **101** has been prepared by reaction of 2-amino-1,3,4-thiadiazole with bromoacetaldehyde (ethanol, reflux) as colorless needles with mp 107°C [80JCS(P2)421].

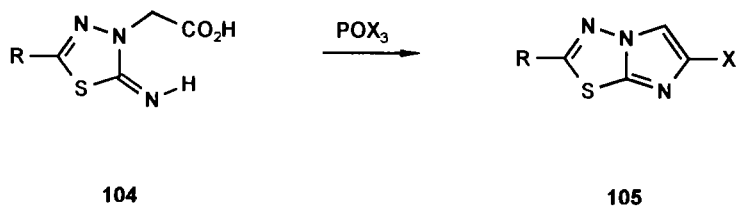
**101**

mp 107 °C

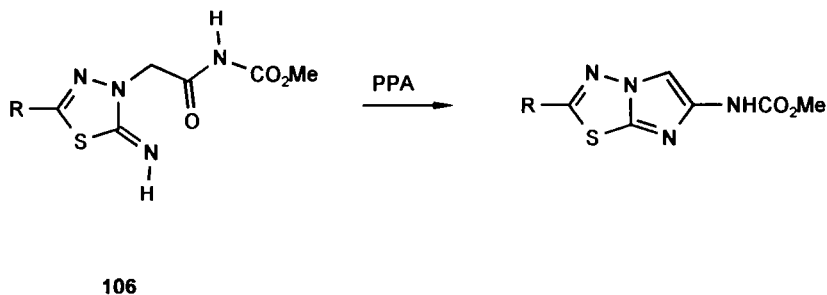
Condensed derivatives are also known. Treatment of 2-amino-1,3,4-thiadiazoles with 2,3-dichloro-1,4-naphthoquinone or 6-chloroquinoline-5,8-dione yields **102** and **103**, respectively (82H333, 91JIC529).

**102****103**

6-Halogeno-substituted imidazo[2,1-*b*][1,3,4]thiadiazoles **105** are accessible from **104** with phosphorus oxytrihalides (toluene, heat) (88JOU1177, 88ZOR1306; 90MI3).



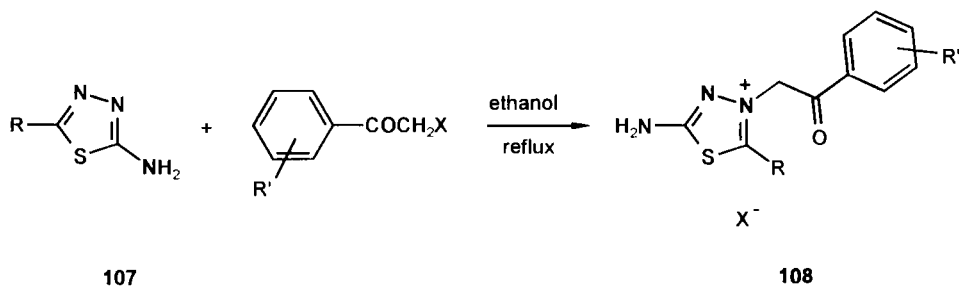
$\text{R} = [4-(4'\text{-alkylcyclohexyl})]\text{C}_6\text{H}_4$ ;  $\text{X} = \text{Cl}, \text{Br}$



$\text{R} = \text{H}, \text{Me}, \text{Et}, n\text{-Bu}, n\text{-PrS}, \text{Ph}$

Carbamates of type **106** on cyclization with PPA (100°C) yield 6-amino derivatives (85FES34; 92FA63).

A report concerning the reaction of 2-amino-1,3,4-thiadiazoles with  $\alpha$ -halo carbonyl compounds seems to be in contradiction with previous studies. DeStevens and co-workers reported (93H763) that 1,3,4-thiadiazoles **107** on reaction with acetophenones gave rise, sometimes in high yield, to a singular product that resisted cyclization in boiling water (75G777), acetic acid, DMF, or PPA (76FES41).

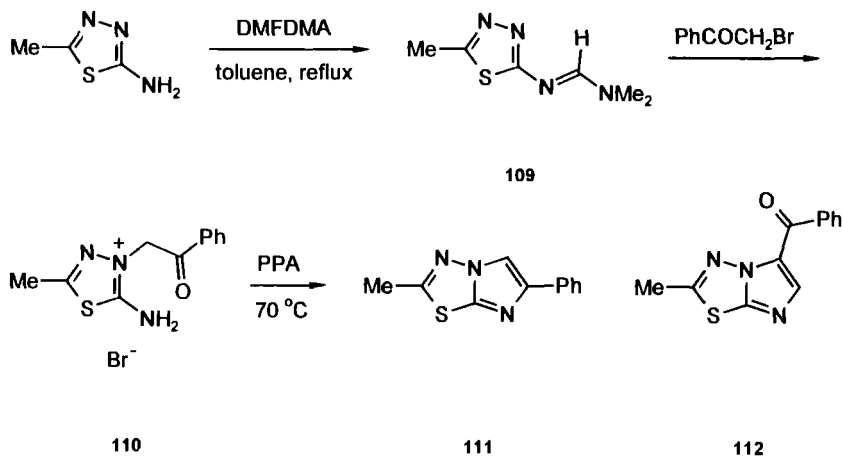


$\text{R} = \text{H}, \text{Me}, \text{Et}, \text{cyclopropyl}$ ;  $\text{R}' = \text{H}, 4\text{-Cl}, 4\text{-OMe}$

$\text{X} = \text{Cl}, \text{Br}$

Because of analytical and spectral data these compounds were formulated as salts **108**. As others (e.g., 52YZ610; 75G777) succeeded in preparing imidazo[2,1-*b*][1,3,4]thiadiazoles with H, Me, or Et in position 2 using exactly the same procedure, this discrepancy remains to be clarified.

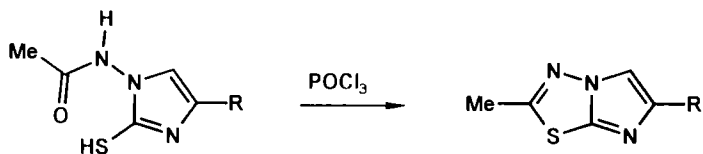
The condensation of  $\alpha$ -halo carbonyl compounds with heterocyclic amines has been used as a convenient method for the preparation of imidazoazines (and azoles). *N*-Heteroaryl formamidines (and formamide oximes) are versatile intermediates for the synthesis of fused heterocycles (82MI2; 83H1591; 84S263). This methodology has also been extended to the preparation of imidazo[2,1-*b*][1,3,4]thiadiazoles (86H379). Treatment of 2-amino-5-methyl-1,3,4-thiadiazole with *N,N*-dimethylformamide dimethyl acetal (DMFDMA) yields **109** quantitatively. Heating this compound with phenacylbromide in chloroform gives **110** (60%), which was transformed to **111** by heating with PPA.<sup>5</sup> However, when **110** was treated with DMFDMA the corresponding hydrobromide was isolated. This material on heating in water undergoes cyclodehydration to produce 5-benzoyl-2-methylimidazo[2,1-*b*][1,3,4]thiadiazole **112**.



## 2. From Imidazoles

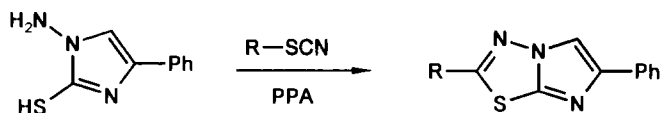
The preparation of imidazo[2,1-*b*][1,3,4]thiadiazoles from imidazoles was reported only in a few cases. Thus treatment of *N*-acetylamino-2-mercaptoimidazole with  $\text{POCl}_3$  yields **113** (63LA113; 77M665). Cyclocondensation of **114** with thiocyanates in PPA gives **115** (94KGS421).

<sup>5</sup> There is a misprint in Scheme 1 of Fajgelj *et al.* (86H379).



113

R = H, Ph



114

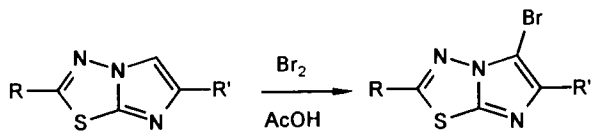
115

R = SMe,  $\text{SCH}_2\text{Ph}$ , SPh

## B. REACTIONS

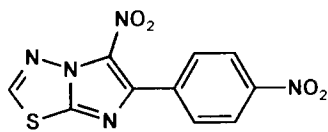
## 1. Reactions at Ring Atoms

Reaction of imidazo[2,1-*b*][1,3,4]thiadiazoles with bromine yields 5-bromo derivatives **117** [72YZ935; 75G777; 83JHC1003; 84FES585; 88JOU172, 88JOU179, 88ZOR192, 88ZOR199; 89IJC(B)500, 89JIC118; 90MI3; 92MI5; 93MI9].

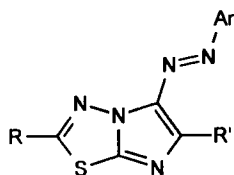


116

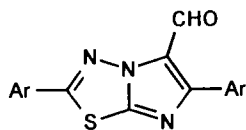
117



118



119



120



Treatment of a hydrobromide with *m*-CPBA also yields a 5-bromo derivative (92FA63). Nitration of **116** ( $R = H$ ,  $R' = Ph$ ) with conc. sulfuric acid/86%/nitric acid (rt, 30 min) affords **118**; a small amount of a mononitro derivative was detected by TLC (75G777). Further examples are given (83JHC1003). Reaction of **116** with diazonium salts gave 5-azo derivatives **119**. In contrast to 6-phenylimidazo[2,1-*b*]thiazole (see Section VI), stable azo compounds are isolated only when strong electrophilic diazonium cations [e.g.,  $(4-NO_2)C_6H_4N_2^+$ ] are employed (75G777).

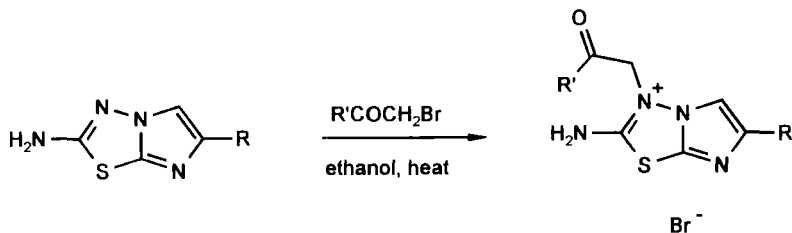
Vilsmeier-Haack reaction of 2,6-diarylimidazo[2,1-*b*][1,3,4]thiadiazoles (DMF,  $POCl_3$ ) yields the corresponding 5-aldehydes **120** (84FES585). Imidazothiadiazoles **121** can also be thiocyanated (72YZ935; 94FES585) (see also Section VI,B,1,a).

**121**

$R = H, Me; R' = Me, Ar$

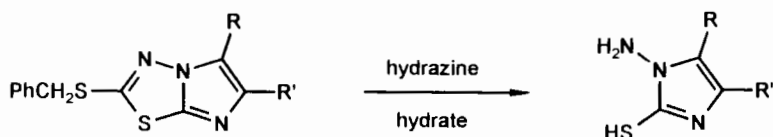
The sulfonylation at C(5) was reported (94MI6).

Alkylation of 2-amino-imidazo[2,1-*b*][1,3,4]thiadiazoles occurs at N(3) (77M665).

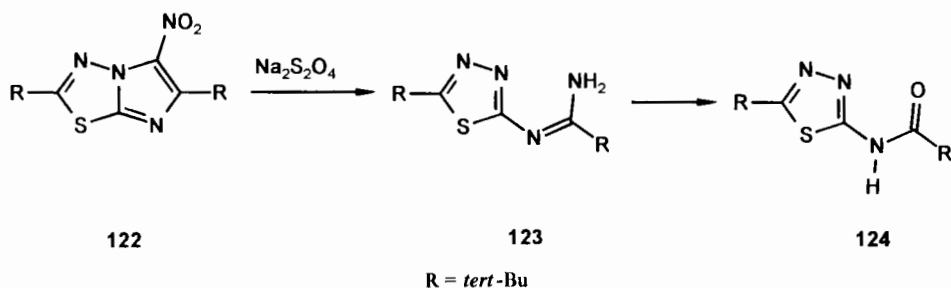


$R = Me, Ph; R' = (4-NO_2)C_6H_4$

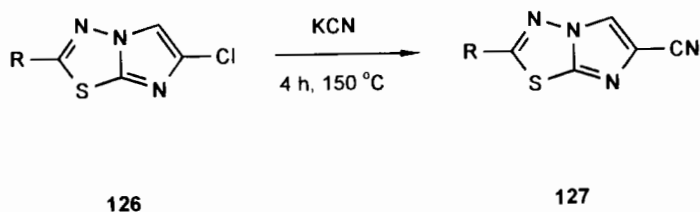
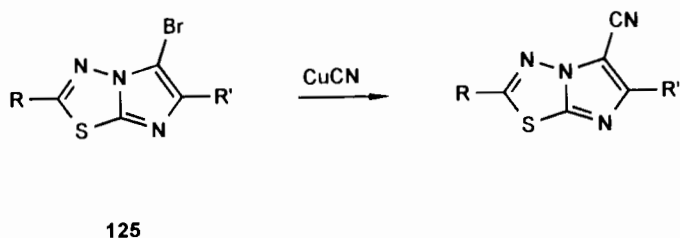
The thiazole ring of imidazo[2,1-*b*][1,3,4]thiadiazoles is cleaved (63LA113; 77M665) on treatment with hydrazine hydrate or with 5 *N* NaOH (80JMC117).



There is one report of reductive cleavage of the imidazole ring. Treatment of **122** with sodium dithionite in aqueous ammonia yielded amidine **123**, which on hydrolysis with acid gave **124**. Compound **124** was obtained directly on reduction with sodium dithionite in aqueous ethanolic sodium bicarbonate (83JHC1003).



Nucleophilic displacement reactions have also been reported. When compounds **125** are reacted with CuCN (DMF or *N*-methylpyrrolidone, heat) nitriles are obtained (83JHC1003; 88JOU179, 88ZOR199; 90MI3).

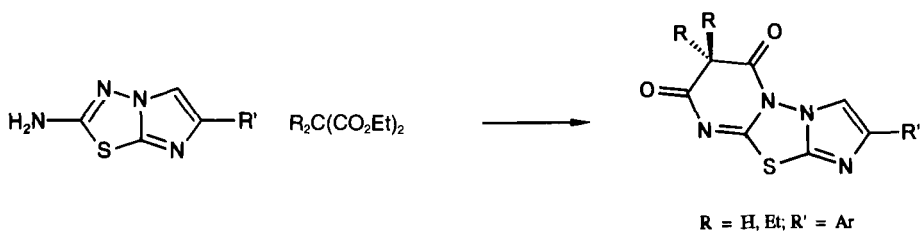


In one case a reductive dehalogenation (disproportionation) was observed (90MI3). See also Section VI,B,1,a and Saldabol and Lando (77ZOR2626).

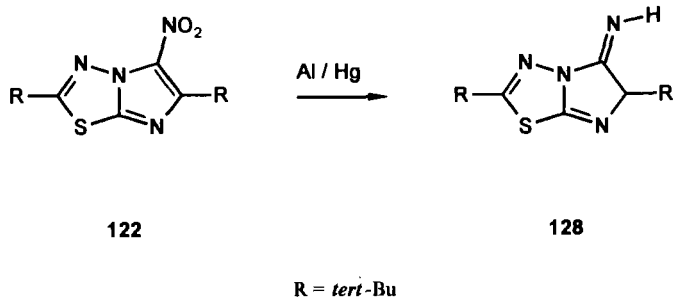
Nucleophilic displacement can also occur at C(6). Treatment of **126** with potassium cyanide yields **127** in low yield (15%) (88JOU1177, 88ZOR1306; 90MI3). The reaction of 2-phenyl-6-bromoimidazo[2,1-*b*][1,3,4]thiadiazole with phenylmercaptan yields the corresponding thioether (94KGS421).

## 2. Side-Chain Reactions

Saponification of side-chain esters yields the corresponding acids (54YZ658; 85FES190). During this reaction decarboxylation may take place (54YZ658). Treatment of esters with hydrazine hydrate yields hydrazides (54YZ658). 2-Aminoimidazo[2,1-*b*][1,3,4]thiadiazoles on treatment with diethyl succinate or diethyl phthalate (PPA, 80°C, 7 h) give the corresponding imides (82AP12). Treatment of 2-amino-imidazo[2,1-*b*][1,3,4]thiadiazoles with diethylmalonate yields tricyclic dihydro-6*H*-imidazo[2,1-*b*][1,3,4]thiadiazolo[3,2*a*]pyrimidinones (82AP12).

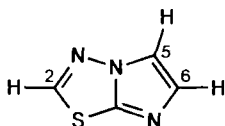


Schiff bases are obtained from 2-aminoimidazothiadiazoles with aldehydes (77M665). Hydrazones and oxime ether formation of imidazothiadiazole-5-carbaldehydes and -5-ketoesters was reported (84FES585; 95EUP662477). Reduction of **122** with Al/Hg yields the tautomeric imine **128** of the corresponding amine (83JHC1003).



## C. SPECTROSCOPIC AND STRUCTURAL STUDIES

The  $^1\text{H}$  NMR spectrum of the parent compound was reported [80JCS(P2)421].



$^1\text{H}$  NMR ( $\text{CDCl}_3$  and  $\text{CF}_3\text{COOH}$ ) (values in ppm):  $\delta(\text{H-2}) = 8.56$  (9.22);  $\delta(\text{H-5}) = 7.82$  (8.20);  $\delta(\text{H-6}) = 7.38$  (7.80);  $J_{56} = 1.42$  (2.45) Hz,  $J_{26} = 0.97$  (1.24) Hz.

As in the case of other bicyclic systems [63ACSA280; 64AJC1128; 65BCJ508, 65JCS4368, 65TL2393; 68JOC1355; 84CHEC(4)973] there is a small W (zigzag) coupling between H(2) and H(6). In line with expectations the chemical shifts appear at lower fields when  $\text{CF}_3\text{COOH}$  is used as solvent (values in parentheses). Examining the  $^1\text{H}$  NMR spectra measured with  $\text{Eu}(\text{fod})_3$  proves that N(7) is the site of complex formation. Protonation, which occurs at N(7), causes significant modification of the geometry with a remarkable enlargement of the angle at N(7).  $^1\text{H}$  NMR spectra of a number of other imidazo[2,1-*b*][1,3,4]thiadiazoles have been reported. Some values are given in Table IX.

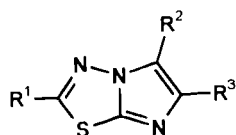
For further values, see Rajeswar Rao *et al.* (86CCC2214), Mohan *et al.* [89IJC(B)500] and Srivastava *et al.* [91IJC(B)620].

IR and UV data have been reported repeatedly but no systematic investigations seem to have been carried out.

A mass spectral fragmentation scheme of 2-alkyl-6-aryl-imidazo[2,1-*b*][1,3,4]thiadiazoles was reported (94IJC(B)585).

There are a few X-ray data of imidazo[2,1-*b*][1,3,4]thiadiazoles available [80JCS(P2)421, 80JMC117, footnote 15]. The thiadiazole rings of **129b** and **130** (Table X) show no significant differences. Protonation, however, causes changes in the bond distances N(4)–C(5), N(4)–C(7a), and C(6)–N(7). Although quantum-chemical calculations, especially when DFT methods (95MI1) are used, are of some reliability in these classes of heterocyclic compounds [96MI1], the bond alteration for C(6)–N(7) is not reproduced properly. Semiempirical methods (AM1, PM3) (90MI1) fail (Table X).

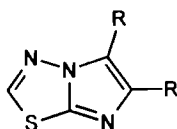
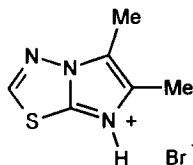
TABLE IX  
<sup>1</sup>H NMR DATA OF IMIDAZO[2,1-*b*][1,3,4]THIADIAZOLES



R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	δ (ppm) <sup>a</sup>	Ref.
H	H	H	H-2: 8.56 H-5: 7.82 H-6: 7.38	80JCS(P2)421
H	H	Me	H-2: 8.47 H-5: 7.54 H-2: 8.54 H-5: 7.60	80JCS(P2)421 75G777
H	Me	Me	H-2: 8.44	80JCS(P2)421
Me	H	Me	H-5: 7.41 H-5: 7.44	80JCS(P2)421 75G777
Me	H	Ph	H-5: 7.97 H-5: 7.85	75G777 86H379
Me	H	(4-NO <sub>2</sub> )C <sub>6</sub> H <sub>4</sub>	H-5: 8.17	86H379
H	H	Ph	H-2: 8.36 H-5: 8.18	86H379
H	H	(4-NO <sub>2</sub> )C <sub>6</sub> H <sub>4</sub>	H-2: 9.28 H-5: 8.96	75G777
H	Br	Ph	H-2: 9.37	75G777
H	NO <sub>2</sub>	(4-NO <sub>2</sub> )C <sub>6</sub> H <sub>4</sub>	H-2: 9.66	75G777
H	H	(4-Me)C <sub>6</sub> H <sub>4</sub>	H-2: 8.53 H-5: 8.13	75G777
H	H	(4-MeO)C <sub>6</sub> H <sub>4</sub>	H-2: 8.57 H-5: 8.10	75G777
H	H	(4-Br)C <sub>6</sub> H <sub>4</sub>	H-2: 8.38 H-5: 8.14	75G777
Me	H	(4-Me)C <sub>6</sub> H <sub>4</sub>	H-5: 7.98	75G777
Me	H	(4-MeO)C <sub>6</sub> H <sub>4</sub>	H-5: 7.84	75G777
Me	H	(4-Br)C <sub>6</sub> H <sub>4</sub>	H-5: 8.67	75G777
(2-Cl)C <sub>6</sub> H <sub>4</sub>	H	(4-Cl)C <sub>6</sub> H <sub>4</sub>	H-5: 8.07	94JJC(B)686
C <sub>5</sub> H <sub>11</sub>	H	(4-Cl)C <sub>6</sub> H <sub>4</sub>	H-5: 7.82	94JCR(S)38
H <sub>2</sub> NO <sub>2</sub> S	H	<i>t</i> Bu	H-5: 7.9 <sup>b</sup>	80JMC117

<sup>a</sup> CDCl<sub>3</sub>.<sup>b</sup> DMSO-*d*<sub>6</sub>.

TABLE X  
BOND DISTANCES OF **129a,b** AND **130** (AM1, PM3, AB INITIO, DFT, EXP.)  
(VALUES IN Å) <96UP1>

**129 a,b****130**

a: R = H, b: R = Me

Method	$r_{12}$	$r_{1,7a}$	$r_{23}$	$r_{34}$	$r_{45}$	$r_{4,7a}$	$r_{56}$	$r_{67}$	$r_{7,7a}$
AM1 <sup>a</sup>	1.738	1.697	1.329	1.336	1.397	1.465	1.411	1.397	1.344
AM1 <sup>a</sup>	1.739	1.699	1.329	1.335	1.406	1.461	1.419	1.407	1.341
AM1 <sup>c</sup>	1.734	1.686	1.332	1.341	1.415	1.438	1.413	1.414	1.365
PM3 <sup>a</sup>	1.779	1.744	1.319	1.389	1.400	1.435	1.388	1.400	1.341
PM3 <sup>b</sup>	1.779	1.745	1.319	1.388	1.406	1.436	1.395	1.406	1.339
PM3 <sup>c</sup>	1.776	1.740	1.319	1.395	1.400	1.419	1.399	1.407	1.374
Ab initio <sup>a,d</sup>	1.757	1.744	1.265	1.352	1.373	1.348	1.355	1.377	1.285
Ab initio <sup>b,d</sup>	1.758	1.745	1.265	1.351	1.382	1.347	1.360	1.386	1.281
Ab initio <sup>c,d</sup>	1.761	1.719	1.264	1.355	1.395	1.316	1.347	1.403	1.317
Ab initio <sup>a,e</sup>	1.742	1.736	1.314	1.363	1.376	1.381	1.384	1.383	1.322
Ab initio <sup>a,f</sup>	1.758	1.742	1.262	1.350	1.374	1.347	1.355	1.378	1.283
Ab initio <sup>b,f</sup>	1.759	1.743	1.262	1.349	1.383	1.346	1.359	1.387	1.279
Ab initio <sup>c,f</sup>	1.761	1.715	1.261	1.352	1.397	1.314	1.345	1.404	1.317
DFT <sup>a,g</sup>	1.768	1.754	1.295	1.362	1.381	1.380	1.377	1.386	1.308
DFT <sup>b,g</sup>	1.770	1.756	1.295	1.361	1.389	1.378	1.384	1.395	1.304
DFT <sup>c,g</sup>	1.776	1.727	1.292	1.364	1.398	1.352	1.373	1.407	1.339
DFT <sup>a,h</sup>	1.768	1.752	1.290	1.360	1.381	1.378	1.375	1.385	1.305
DFT <sup>b,h</sup>	1.769	1.753	1.291	1.359	1.389	1.376	1.382	1.394	1.301
DFT <sup>c,h</sup>	1.775	1.724	1.287	1.361	1.399	1.349	1.370	1.407	1.337
Exp. <sup>h,i</sup>	1.740	1.720	1.288	1.383	1.376	1.354	1.374	1.399	1.322
Exp. <sup>c,i</sup>	1.737	1.711	1.276	1.375	1.405	1.328	1.353	1.379	1.326

<sup>a</sup> **129a.**<sup>b</sup> **129b.**<sup>c</sup> **130.**<sup>d</sup> RHF/6-31G\*.<sup>e</sup> MP2/6-31G\*.<sup>f</sup> RHF/6-311G\*\*.<sup>g</sup> Becke3LYP/6-31G\*.<sup>h</sup> Becke3LYP/6-311G\*\*.<sup>i</sup> 80JCS(P2)421.

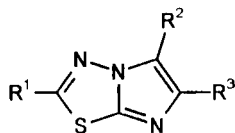
## D. APPLICATIONS

1. *Biological Activity*

The biological activity of imidazo[2,1-*b*][1,3,4]thiadiazoles has been investigated in some detail. Some results are given in Table XI.

2. *New Materials*

a. *Liquid Crystals*. In recent years imidazo[2,1-*b*][1,3,4]thiadiazoles (and other 5,5-systems) have attracted considerable interest as core elements of liquid crystals (88JOU172, 88JOU179, 88ZOR192, 88ZOR199; 90MI3; 96UP1). Ivashchenko and co-workers succeeded in preparing liquid crystalline imidazothiadiazoles. These new mesogens normally have a wide mesophase range and a high thermal stability.



R<sup>1</sup>: 4-alkylcyclohexyl, (4-alkyl)C<sub>6</sub>H<sub>4</sub>

R<sup>2</sup>: H, alkyl Br, CN

R<sup>3</sup>: 4-(4'-alkylcyclohexyl)C<sub>6</sub>H<sub>4</sub>

TABLE XI  
BIOLOGICAL PROPERTIES OF IMIDAZO[2,1-*b*][1,3,4]THIA DIAZOLES

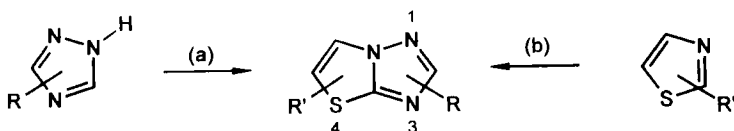
Biological function	Ref.
Herbicidal activity	94MI6
Biological activity	93MI10
Antibacterial and antifungal activity	89JIC118; 93MIP1; 93MI9
As angiotensin II receptor antagonists	93MIP1
Fungicidal activity	91IJC(B)620; 95EUP622477
Antimicrobial activity	72GEP2109577; 90FA1341
Inhibition of the enzyme activity of 3',5'-nucleotide phosphodiesterase	69GEP1809013
Sulfonamide derivatives as therapeutic agents	77BP1464259
Anti-inflammatory activity	85FES190
Diuretic activity	94AF618
Ionotropic activity	94MI4
Bactericidal activity	82JIC1170
Antimycotic activity	84FES585
Anti-bactericidal activity	84FES585
Anthelmintic activity	85FES34; 89FA671; 92FA63

b. *Dyes*. Cyanine dyes with imidazo[2,1-*b*][1,3,4]thiadiazole moieties have been described in the patent literature (69GEP1804465; 71USP 3615639; 74USP3809691).

## VIII. Thiazolo[3,2-*b*][1,2,4]-triazoles

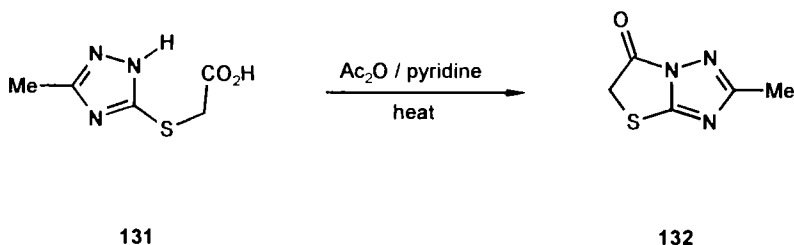
### A. SYNTHESIS

Thiazolo[3,2-*b*][1,2,4]triazoles have been prepared either from suitably substituted 1,2,4-triazoles [route (a)] or from 1,3-thiazoles [route (b)].

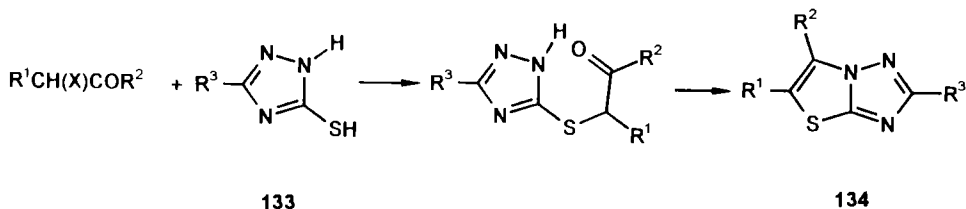


#### 1. From 1,2,4-Triazoles

The ring closure of *S*-alkylated 3-mercapto-1,2,4-triazoles to thiazolo[3,2-*b*][1,2,4]triazoles was reported a long time ago. Thus, treatment of **131** with acetic anhydride/pyridine (heat) yields **132** (50BRP634951).



Mercaptotriazoles **133**, available from thiosemicarbazones, are versatile starting materials for the preparation of thiazolo[3,2-*b*][1,2,4]triazoles. Treatment with  $\alpha$ -halo ketones (and esters) yields *S*-alkylated derivatives that are cyclized to **134** either directly or on treatment with acidic catalysts (e.g.,  $P_2O_5/H_3PO_4$ ).



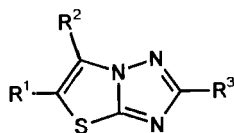


In Table XII some selected examples that have been prepared by this method are given.

Potts and Husain reported (71JOC10) that a 5-substituent on the triazole has a pronounced influence on the ease of ring closure. Thus, **135** with chloroacetone or phenacyl bromide gave **136** in greater than 70% yield using a 4-h reaction period (reflux). Under the same conditions **137** gave the intermediate products **138**; increasing the reaction time to 24 h furnishes the corresponding thiazolo[3,2-*b*][1,2,4]triazoles directly. Cyclization of **138** with POCl<sub>3</sub> (xylene, reflux, 8h) was reported to yield the *isomeric* thiazolo[2,3-*c*][1,2,4]triazole **139**.

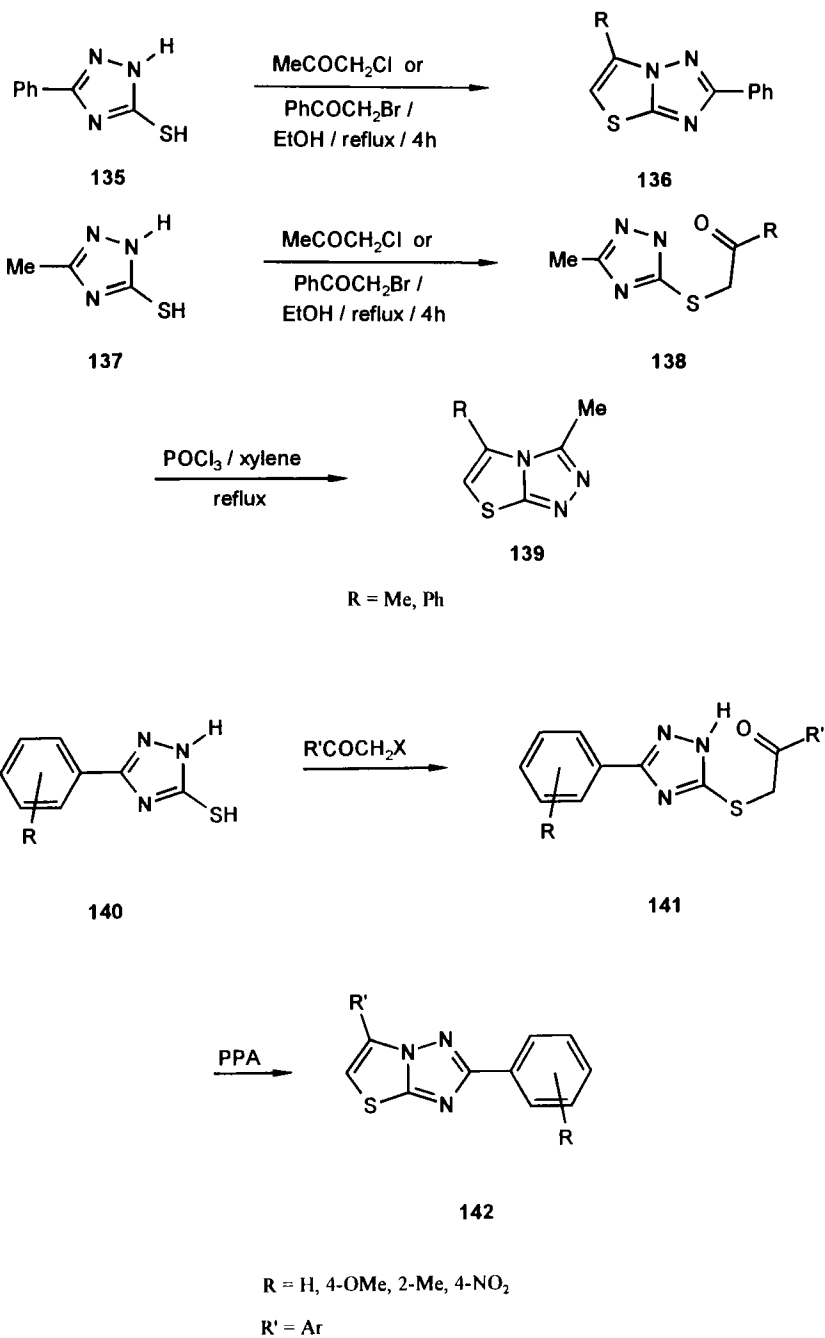
These observations are at some variance with later findings (74IJC485). Thus, **140** on heating with  $\alpha$ -halo ketones in anhydrous ethanol gave the uncyclized ketones **141**, which underwent PPA cyclization, giving thiazolo[3,2-*b*][1,2,4]triazoles **142** and *not* thiazolo[2,3-*c*][1,2,4]triazoles. Cyclization of **141** [R = H, R' = (4-Br)C<sub>6</sub>H<sub>4</sub>] with POCl<sub>3</sub> or PPA gave the same product [**142**, R = H, R' = (4-Br)C<sub>6</sub>H<sub>4</sub>]. See also Gupta *et al.* [77IJC(B)1143].

TABLE XII  
THIAZOLO[3,2-*b*][1,2,4]TRIAZOLES

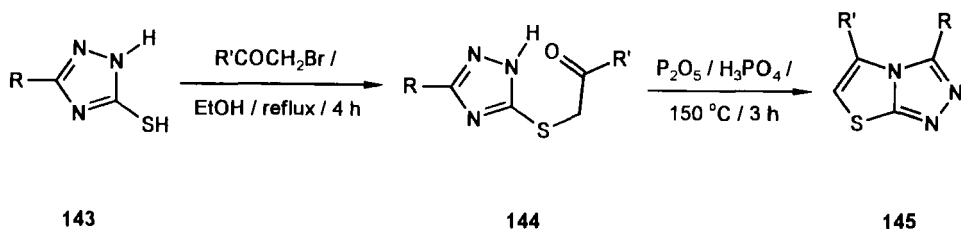


R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Ref.
H	( <i>o</i> , <i>m</i> , <i>p</i> -RO)Ph	( <i>o</i> , <i>m</i> , <i>p</i> -alkyl, <i>O</i> -alkyl)Ph	93FA707
H	Ar	H	71JCS(C)1667; 72YZ935; 86JHC1531
H	Ar	Me, Et	72YZ935; 78IJC(B)475
H	Ar	Naphthyl ( $\alpha,\beta$ )	90IJC(B)88; 92JIC268
H	H	Ph	87AP528
H	Ar	Ar	71JOC10; 74IJC485; 77IJC(B)1143; 82IJC(B)243; 82MI3; 83IJC(B)249; 85IJC(B)808; 85IJC(B)1221; 86JHC1439; 87IJC(B)526; 87PJC547; 91MI1
H	Styryl	H	86JHC1531
H	Ar	Imidazolonyl	67MI1
H	Ribosyl	NH <sub>2</sub>	92SC2815
H	2-Coumarinyl	Ar	81AP435; 94IJC(B)579
H	Ph	2-Furyl	72JMC332 <sup>a</sup>

<sup>a</sup> There is a misprint in the Experimental section.



Jain and Handa reported [82IJC(B)732] that the mode of ring closure may depend critically on the 5-substituent of the triazole. 3-Mercapto-5-(4'-pyridyl)[1,2,4]triazole **143** was reacted with phenacyl bromides to give **144**, which on treatment with PPA resulted in the formation of thiazolo[2,3-*c*][1,3,4]triazoles **145**. The structure of **145** [ $R' = (4\text{-Cl})\text{C}_6\text{H}_4$ ] was proved by an independent synthesis starting with isonicotinyl thiosemicarbazide.

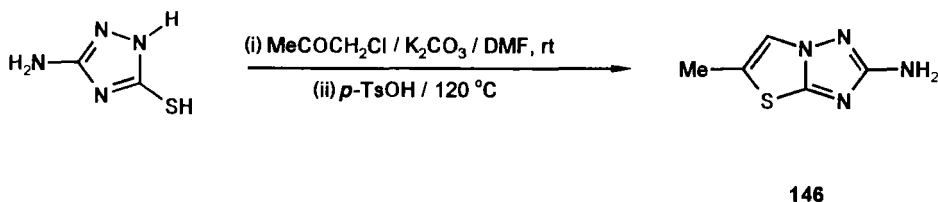


$R = 4\text{-pyridyl}; R' = (\text{H}, 4\text{-Cl}, 4\text{-NO}_2, 4\text{-ph}, 3\text{-NO}_2)\text{aryl}$

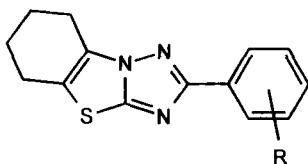
Discrepancies concerning the ease of cyclization have also been reported by other authors [67MI1; 71JCS(C)1667].

For further examples of thiazolo[3,2-*b*][1,2,4]triazoles, see several references [72JMC332; 85IJC(B)1221; 86JHC1439; 88CAT91].

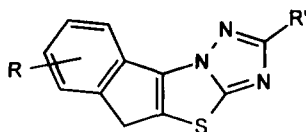
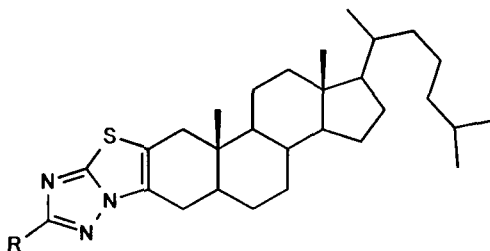
Coumarinyl-substituted thiazolo[3,2-*b*][1,2,4]triazoles have also been reported. They are available in one step by reaction of 5-aryl-3-mercapto[1,2,4]triazoles with 3-bromoacetyl coumarin (ethanol, reflux, 8 h; yield 44–65%) (81AP435) or in a two-step reaction from the corresponding *S*-alkylated intermediates with PPA [93MI2; 94IJC(B)579]. 2-Aminothiazolo[3,2-*b*][1,2,4]triazoles are also available from 3-mercaptotriazoles. Treatment of 5-amino-3-mercaptotriazole with chloroacetone (DMF,  $\text{K}_2\text{CO}_3$ ) and subsequent acid-catalyzed cyclization yields **146** [90JAP(K)02/142797].



Cyclic  $\alpha$ -halo ketones give condensed systems, such as **147** [80IJC(B)260], **148** [93IJC(B)1187], and **149** [80JCS(P1)2146].

**147**

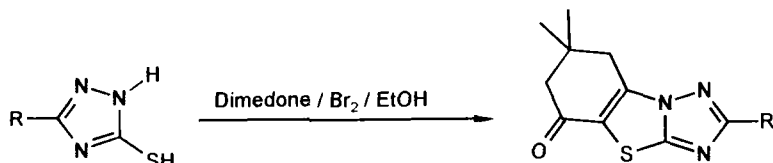
R = H, 2-Cl, 4-Cl, 3-Me, 4-Me, 4-OMe

**148**R = OMe, OEt; R' = Ar, PhCH<sub>2</sub>**149**

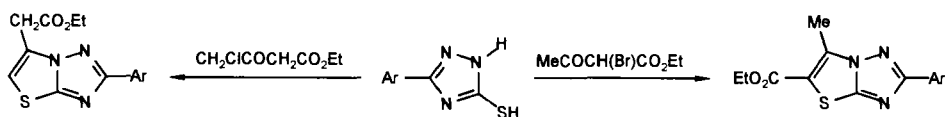
R = H, Me

2-Bromo-3-hydroxy-1,4-naphthoquinone (bromolawsone) and 2,3-dichloro-1,4-naphthoquinone react similarly [93CCC1191, 93IJC(B)365]. Further examples have been reported (85MI1).

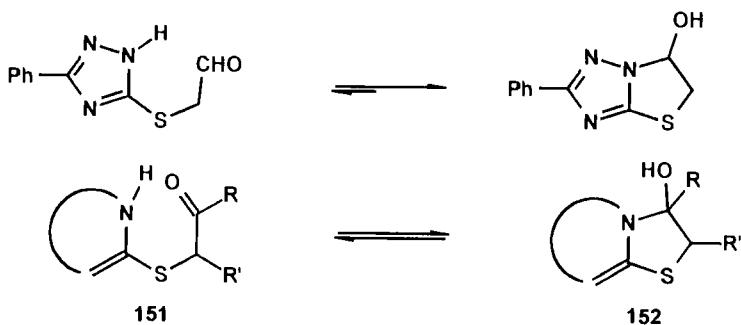
The  $\alpha$ -halo ketone compound has also been prepared *in situ*. Dimedone reacts with 2-mercaptotriazoles in the presence of bromine to give **150** (91H231).

**150**

2-Bromo- and 4-chloroacetoacetic ethyl ester react in the same manner as do  $\alpha$ -halo ketones (78JHC401; 80JHC1321; 91AP49).

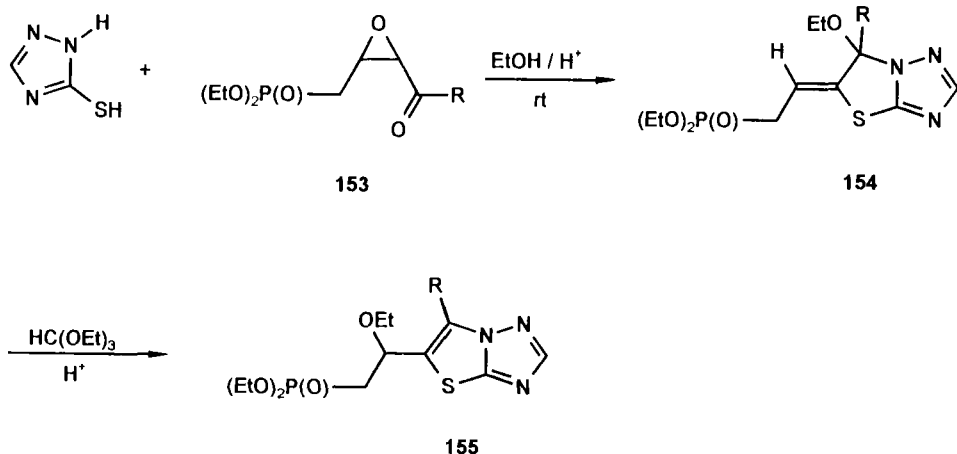


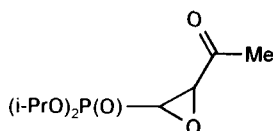
As reported by Simiti and co-workers (87AP528) the *S*-alkylated product of 5-phenyl-3-mercapto-1,2,4-triazole with chloroacetaldehyde exists exclusively as the hydroxythiazoline.



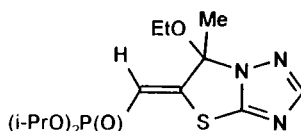
With conc. sulfuric acid the corresponding thiazolo[3,2-*b*][1,2,4]triazole is obtained. A tautomeric equilibrium of the type **151**  $\rightleftharpoons$  **152** is well known for other heterocycles [77HC(30)1].

Zbiral and co-workers reported on the reaction of mercaptotriazole with epoxyphosphonates **153** in acidic ethanol (88CB977).





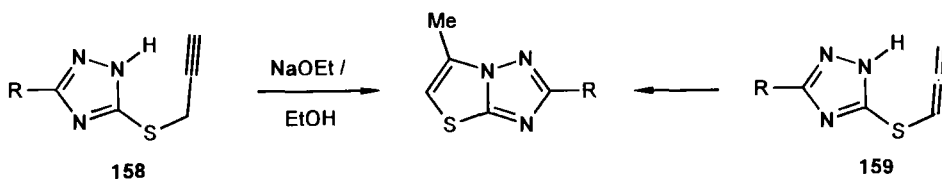
156

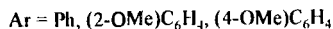
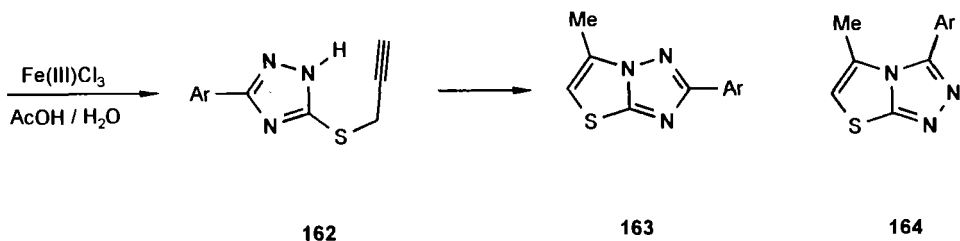
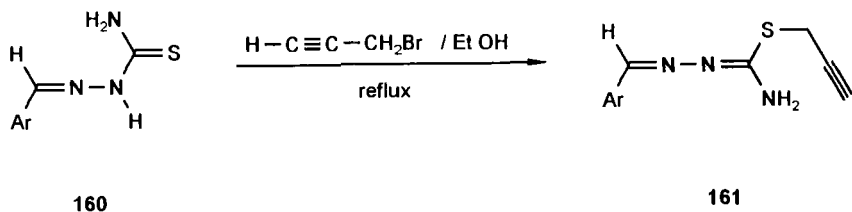


157

Nucleophilic ring opening of the epoxide with subsequent ring closure yields **154**, which on treatment with triethoxymethane/ $H^+$  rearranges to **155**. With epoxyphosphonate **156** compound **157** is obtained. An allylic rearrangement of this product was not observed. Thiazolo[3,2-*b*][1,2,4]triazoles have also been prepared by base-catalyzed cyclization of 3-propynylthio-1,2,4-triazoles, which are in turn available from 3-mercaptoprop-1,2,4-triazoles (72YZ935; 79S52).

In an attempt to prepare 3-propynylthio-5-substituted 1,2,4-triazoles other authors encountered the formation of 3-allenylthiotriazoles, perhaps through an intermediate 3-propynylthio derivative [77IJC(B)220; 78S288]. However, the use of sodium acetate instead of sodium hydroxide prevented this rearrangement and the *S*-alkylated products were obtained in 60–70% yield. The corresponding thiazolo[3,2-*b*]-*s*-thiazoles can also be prepared by treatment of **158** with  $Hg(OAc)_2$  (yield 40–50%). Subsequently, it was found that the *S*-allenyl-1,2,4-triazoles **159** can also be cyclized using sodium methoxide in methanol [81IJC(B)161] (yield 70%). Interestingly, in the series of 2-(2-propynylthio)benzimidazoles the course of cyclization may depend on the catalyst ( $NaOEt/EtOH$  or  $Hg(OAc)_2$  (76S189)). If an *S*-alkenyl-1,2,4-triazole is treated with conc. sulfuric acid, a dihydrothiazolo[3,2-*b*][1,2,4]triazole is obtained (87AP528). Miocque and co-workers developed a synthesis of thiazolo[3,2-*b*][1,2,4]triazoles starting from the readily available arylaldehyde thiosemicarbazones **160**. These compounds are converted into the propynyl derivatives **161** by reaction with 3-bromopropyne in *neutral* medium (ethanol, reflux); this prevents the propyne–allene isomerization. On cyclodehydrogenation with iron (III) chloride in acetic acid the triazoles are obtained. Heating **162** in alkaline or acidic medium leads to the thiazolotriazoles **163** and **164** (79S52).

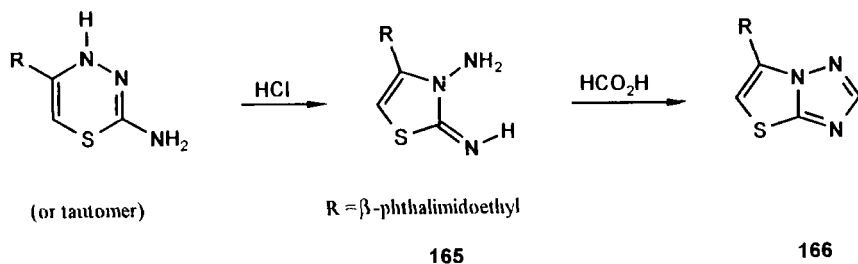




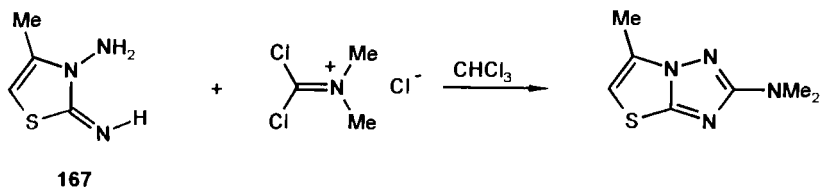
## 2. From Thiazoles

It has been claimed in the early literature that the parent ring system is available by cyclization of 2-(*N*-methylimino)-3-nitroso-2,3-dihydrothiazole with diluted hydrochloric acid (1891LA108), but the structural assignment has been questioned [61HC(15)203; 74JHC459].

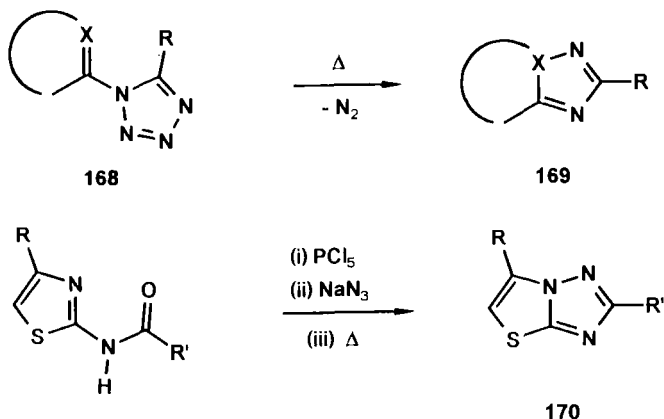
There is an early report that a substituted thiazolo[3,2-*b*]-*s*-triazole **166** is formed when a 3-amino-2,3-dihydrothiazole **165** is reacted with formic acid (60MI1, 60PHA226).



Hervens and Viehe treated **167** with *N*-(dichloromethylene)-*N,N*-dimethylammonium chloride (CHCl<sub>3</sub>, reflux) and obtained a thiazolotriazole in 93% yield (73AG446; 73AGE405).



The thermolysis of tetrazoles **168** may result in the formation of mono- and bicyclic heterocycles **169**.

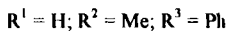
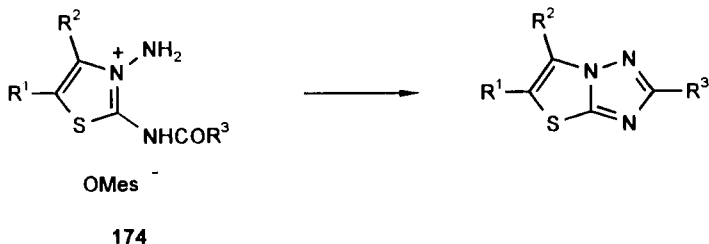
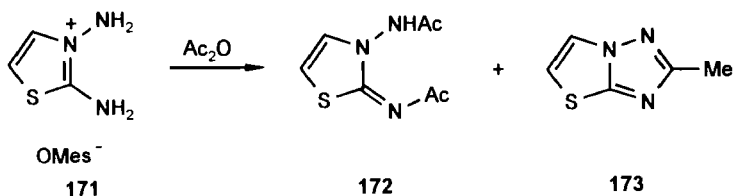


R, R' = Ph, (2-Br)C<sub>6</sub>H<sub>4</sub>, (4-Cl)C<sub>6</sub>H<sub>4</sub>, (4-Me)C<sub>6</sub>H<sub>4</sub>, (4-OMe)C<sub>6</sub>H<sub>4</sub>, (4-NO<sub>2</sub>)C<sub>6</sub>H<sub>4</sub>

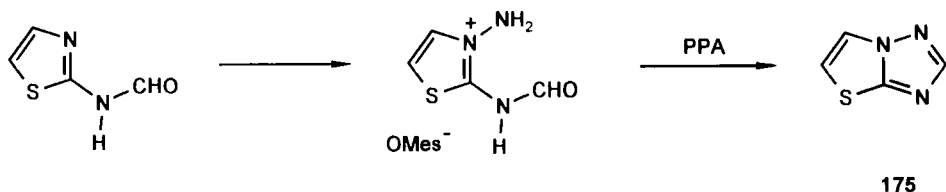
This reaction is of broad applicability (e.g., 1,3,4-oxadiazoles [94HOU526] and benzoanalogs of thiazolo[3,2-*b*][1,2,4]triazoles [83IJC(B)1194]. 2,5-Diarylthiazolo[3,2-*b*][1,2,4]triazoles have also been prepared by this route. 2-Aminothiazoles are acylated and subsequently transformed to the triazole. Pyrolysis of these compounds in boiling decalin (2 h) furnishes **170** (yield 44–64%) [85IJC(B)808]. Using this methodology condensed derivatives also are available (91JIC420).

A further synthesis of thiazolo[3,2-*b*][1,2,4]triazoles starts with 2,3-diaminothiazoles. Treatment of 2-aminothiazole with *O*-mesitylsulfonylhydroxylamine results in the formation of salt **171**, which on heating with acetic anhydride (140–150°C) gives a mixture of **172** and **173**. 2-Phenylthiazolo[3,2-*b*]-*s*-triazole could be obtained from **171** and benzoylchloride (~200°C) in 68% yield. When 2-acylamino-3-aminothiazolium salts **174** are heated 20–30°C above their melting point for 1 h the corresponding thiazolo[3,2-*b*]-*s*-triazoles were obtained. Much better results were achieved by using PPA (100–110°C, 1.5 h; 97% yield) (73JHC947).

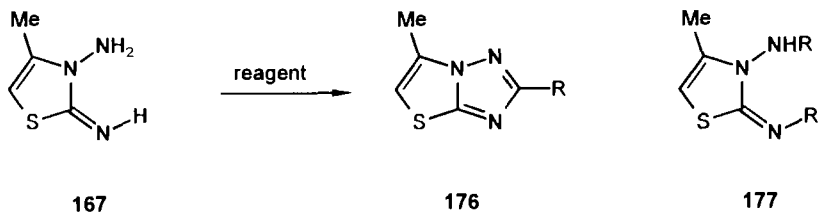




The parent system **175** was prepared in 90% yield by cyclization of 3-amino-2-formamido thiazolium mesitylene sulfonate, which, in turn, was readily obtained by reaction of 2-formamido-thiazole with *O*-mesitylsulfonylhydroxylamines (colorless crystals with mp 98–100°C). The hydrochloride was prepared by passing dry hydrogen chloride into an ethereal solution of **175** (mp 226–227°C) (74JHC459).



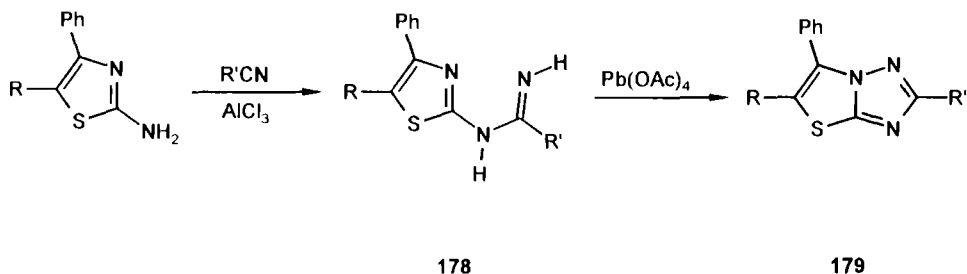
Ring closure of **167** to thiazolo[3,2-*b*][1,2,4]triazoles can also be effected by acid anhydride, but the course of the reaction depends on the starting materials. Refluxing **167** with acetic or propionic anhydride (3–4 h) leads directly to **176**. With pentafluoropropionic, heptafluorobutanic, and benzoic anhydride only diacetylated products **177** were produced (further details [76JHC(13)1225]).



reagent =  $\text{Ac}_2\text{O}$ ,  $(\text{EtCO})_2\text{O}$ ,  $\text{HC}(\text{OEt})_3$ ,  $\text{CNBr}$ ,  $\text{CS}_2$

Cyclization of **167** with ethyl orthoformate leads to **176** ( $\text{R} = \text{H}$ , 36%). With cyanogen bromide in refluxing methanol **176** ( $\text{R} = \text{NH}_2$ ) is obtained in only 10% yield. Reaction of **167** with carbon disulfide (methanol,  $\text{H}_2\text{O}$ ,  $\text{KOH}$ , reflux) leads to the 5-methylthiazolo[3,2-*b*][1,2,4]triazole-2-thiol (**176**,  $\text{R} = \text{SH}$ ), which was readily converted to **176** ( $\text{R} = \text{SMe}$ ) with methyl iodide [76JHC(13)1225].

2-Hydroxythiazolo[3,2-*b*][1,2,4]triazoles (**176**,  $\text{R} = \text{OH}$ ) are also available by this route. Treating **167** with methyl chloroformate (sodium hydroxide) and subsequently with sodium methoxide yields **176** ( $\text{R} = \text{OH}$ ) (71GEP1942015; 72GEP2032173, 72USP3682943). Thiazolo[3,2-*b*][1,2,4]triazoles are also available from 2-aminothiazoles via amidines **178**. Lead tetra-acetate dehydrogenation of **178** leads to **179** (94MI1).

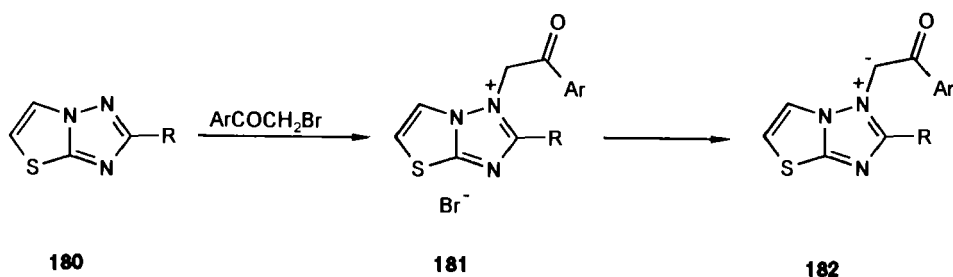


$\text{R} = \text{Ar-N}=\text{N}-$ ;  $\text{R}' = \text{Ar}$

## B. REACTIONS

### 1. Reactions at Ring Atoms

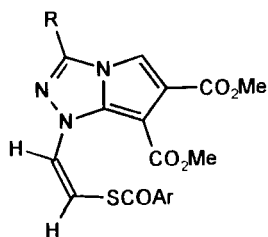
Alkylation of thiazolo[3,2-*b*][1,2,4]triazoles takes place at N(1). Treatment of **180** with 2-bromo-1-arylethanones (acetone, heating) yields **181** [94JAP(K)06/184165, 94TL4587].



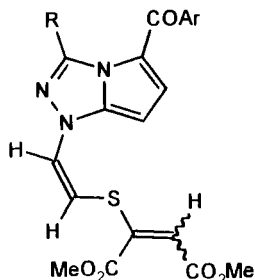
R = H, Me

Ar = Ph, (4-Me)C<sub>6</sub>H<sub>4</sub>, (4-OMe)C<sub>6</sub>H<sub>4</sub>, (4-Cl)C<sub>6</sub>H<sub>4</sub>,  
(4-Br)C<sub>6</sub>H<sub>4</sub>, (4-NO<sub>2</sub>)C<sub>6</sub>H<sub>4</sub>

These compounds are used for the preparation (Et<sub>3</sub>N, MeCN) of the corresponding ylides **182**. These ylides with DMAD give **183** and **184** (*E/Z* mixture). Compound **183** seems to be formed by a new type of intramolecular benzoyl migration of an intermediate 1:1 adduct.



**183**

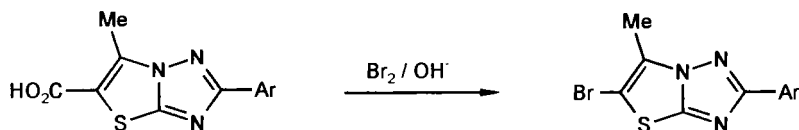


**184**

The 1:2 adduct **184** has a side chain similar to that of a product obtained from the reaction of dihydroimidazo[2,1-*b*]thiazolium ylides and DMAD (92JOC2347).

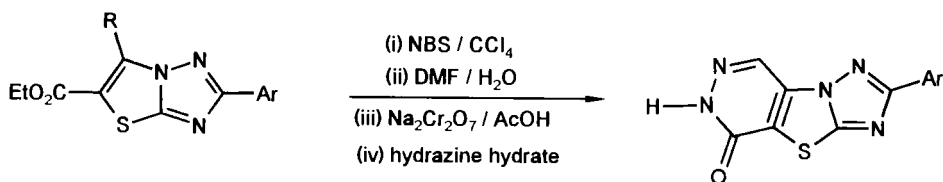
## 2. Side-Chain Reactions

2-Arylthiazole-5-carboxylic acids on treatment with base and bromine yield the corresponding 5-bromothiazole (76AP128). The same behavior is observed for thiazolo[3,2-*b*][1,2,4]triazoles (91AP49; 94MI2).

**185**Ar = Ph, (4-Cl)C<sub>6</sub>H<sub>4</sub>

Compound **185** can also be obtained by direct bromination of the corresponding thiazolo[3,2-*b*][1,2,4]triazole (Br<sub>2</sub>, acetic acid) (91AP49). Bromination at C-5 can also be affected by bromine/NBS in chloroform (72YZ935). Thiocyanation, which was possible in the imidazo[2,1-*b*]thiazole and -[1,3,4]thiadiazole series (see Sections VI,B,1,a and VII,B,1) failed (72YZ935).

Esters of thiazolo[3,2-*b*][1,2,4]triazoles are hydrolyzed in the usual manner (80JHC1321; 91AP49; 92AP609). Side-chain bromination of **186** (R = Me) with NBS yields **186** (R = CH<sub>2</sub>Br); hydrolysis (DMF/H<sub>2</sub>O, reflux) furnishes the corresponding carbinol. Oxidation of this compound (Na<sub>2</sub>Cr<sub>2</sub>O<sub>7</sub>/AcOH) yields an aldehyde that reacts with hydrazine to give a 1,2,4-triazolo[2',3'-3,2]triazolo[4,5-*d*]pyridazinone **187** (92AP609).

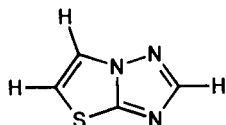
**186****187**

2-Hydroxythiazolo[3,2-*b*][1,2,4]triazoles (or the corresponding tautomers) can be readily *O*-acylated (71GEP1942015; 72GEP2032173, 72USP3682943; 74GEP2323720; 75GEP2350631, 75GEP2361451, 75GEP2428204).

2-Aminothiazolo[3,2-*b*][1,2,4]triazoles are readily bis-*N*-acylated (Ac<sub>2</sub>O, reflux). The *S*-alkylation of thiazolo[3,2-*b*][1,2,4]triazoles with chloro- and acetoxymethylcephem was also reported (91MI2). An *S*-alkylated thiazolo[3,2-*b*][1,2,4]triazole was converted to a sulfonyl chloride and aminated (88EUP244098).

## C. SPECTROSCOPIC PROPERTIES

Spectral data of the parent compound have been reported (74JHC459).



$^1\text{H}$  NMR ( $\text{CDCl}_3$ )<sup>6</sup>:  $\delta(\text{H-6}) = 6.98$  ppm (dd,  $J_1 = 4.3$  Hz,  $J_2 = 1.4$  Hz),  $\delta(\text{H-5}) = 7.80$  (d),  $\delta(\text{H-2}) = 8.10$

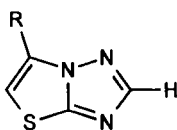
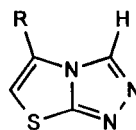
IR (KCl):  $1450\text{ cm}^{-1}$  (s),  $1390$  (s),  $1380$  (s),  $1340$  (s)

UV [ $\lambda_{\text{max}}$  (lg  $\epsilon$ )] (MeOH):  $242\text{ nm}$  (3.88),  $247$  (sh, 3.73)

The  $^1\text{H}$ -NMR spectrum shows a long-range coupling of H(6) with H(2). Analogous couplings between protons separated by six bonds in a W path (zigzag path) have also been reported for other bicyclic systems [63ACSA280; 64AJC1128; 65BCJ508, 65JCS4368, 65TL2393; 68JOC1355; 84CHEC(4)973].

In Table XIII, some  $^1\text{H}$  NMR data of substituted thiazolo[3,2-*b*][1,2,4]triazoles are given.

Thiazolo[3,2-*b*][1,2,4]triazoles (**188**) and thiazolo[2,3-*c*][1,2,4]triazoles (**189**) can be distinguished [87IJC(B)526] by comparing the signal of the triazole proton: In **189** this signal always appears *downfield* compared to that in **188**. The triazole proton is observed at  $\delta = 8.13$  ppm (for **188**, R = Me) and  $\delta = 8.60$  ppm (for **189**, R = Me) [80JCS(P1)2146].

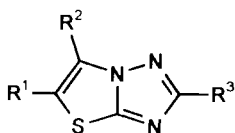
**188****189**

IR spectra of thiazolo[3,2-*b*][1,2,4]triazoles do not seem to have been investigated systematically. Some data are given in Table XIV.

For further IR data see several references [81IJC(B)161; 82IJC(B)243; 83IJC(B)249; 85IJC(B)1221; 90IJC(B)88].

<sup>6</sup>  $\delta$ -Values taken from Fig. 1 in Tamura *et al.* (74JHC459).

TABLE XIII  
<sup>1</sup>H-NMR DATA OF THIAZOLO[3,2-*b*][1,3,4]TRIAZOLES (VALUES IN PPM)



R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	δ(H-2)	δ(H-5)	δ(H-6)	Ref.
H <sup>a</sup>	Me	H	8.12	6.63	—	76JHC(13)1225
H <sup>a</sup>	Me	Me	—	6.50	—	76JHC(13)1225
H <sup>a</sup>	Me	Et	—	6.40	—	76JHC(13)1225
H <sup>a</sup>	Me	CF <sub>3</sub>	—	6.80	—	76JHC(13)1225
H <sup>a</sup>	Me	NH <sub>2</sub>	—	6.77	—	76JHC(13)1225
H <sup>a</sup>	Me	NHAc	—	7.10	—	76JHC(13)1225
H <sup>a</sup>	Me	SMe	—	6.52	—	76JHC(13)1225
H <sup>b</sup>	Me	Me	—	6.55	—	71JOC10
H <sup>b</sup>	Me	Ph	—	6.50	—	71JOC10
H <sup>b</sup>	Ph	Ph	—	6.52	—	71JOC10
H <sup>b</sup>	Ph	Me	—	6.99	—	71JOC10
H <sup>a</sup>	H	Me	—	6.91 <sup>c</sup>	7.69 <sup>c</sup>	73JHC947
H <sup>a</sup>	H	Ph	—	—	—	73JHC947
H <sup>a</sup>	Me	Ph	—	6.50 <sup>f</sup>	—	73JHC947
H <sup>a</sup>	Ph	H	8.50 <sup>d</sup>	—	7.66 <sup>d</sup>	86JHC1531
H <sup>a</sup>	<i>trans</i> -Styryl	H	8.42 <sup>d</sup>	—	7.62 <sup>d</sup>	86JHC1531
H <sup>a</sup>	Me	Ph	—	6.50	—	79S52
H <sup>a</sup>	Me	(2-OCH <sub>3</sub> )C <sub>6</sub> H <sub>4</sub>	—	6.55	—	79S52
H <sup>a</sup>	Me	(4-OCH <sub>3</sub> )C <sub>6</sub> H <sub>4</sub>	—	6.45	—	79S52
H <sup>a</sup>	(4-Br)C <sub>6</sub> H <sub>4</sub>	Ph	—	7.13	—	74IJC485
H <sup>a</sup>	CH <sub>2</sub> CO <sub>2</sub> Et	Ph	—	7.15	—	78JHC401
H <sup>a</sup>	(4-Br)C <sub>6</sub> H <sub>4</sub>	(4-Me)C <sub>6</sub> H <sub>4</sub>	—	6.93	—	82IJC(B)243
			—	7.59 <sup>g</sup>	—	85IJC(B)1221
H <sup>a</sup>	(4-Cl)C <sub>6</sub> H <sub>4</sub>	(4-Me)C <sub>6</sub> H <sub>4</sub>	—	6.94	—	83IJC(B)249
H <sup>c</sup>	(4-NO <sub>2</sub> )C <sub>6</sub> H <sub>4</sub>	α-Naphthyl	—	7.45	—	90IJC(B)88
H <sup>a</sup>	Me	H	—	—	—	—

<sup>a</sup> DMSO-*d*<sub>6</sub>.

<sup>b</sup> CDCl<sub>3</sub>.

<sup>c</sup> *J* = 5 Hz.

<sup>d</sup> Singlet.

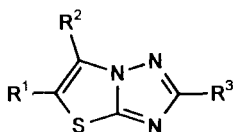
<sup>e</sup> TFA.

<sup>f</sup> In [81IJC(B)161] δ = 6.26 ppm is reported (solvent not given).

<sup>g</sup> TFA-CDCl<sub>3</sub>.

Both the parent compound and the alkyl-substituted thiazolo[3,2-*b*][1,2,4]triazoles show UV absorption between 240 and 250 nm. Some UV data of other derivatives are given in Table XV.

TABLE XIV  
IR DATA OF THIAZOLO[3,2-*b*][1,2,4]TRIAZOLES



R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	$\nu$ (cm <sup>-1</sup> )	Ref.
H	Me	Me	3075, 3000, 1575, 1495	71JOC10
H	Me	Ph	3100, 1475, 1400	71JOC10
H	Ph	Ph	3050, 1500, 1470	71JOC10
H	Ph	Me	3050, 1550, 1495	71JOC10
H	H	Me	3100, 1540, 1510, 1470, 1430, 1300	73JHC947
H	H	Ph	3100, 2900, 1530, 1460, 1440, 1330	73JHC947
-CH = CH - CH = CH-		Me	3050, 2900, 1600, 1490, 1450, 1300	73JHC947
-CH = CH - CH = CH-		Ph	3050, 1600, 1470, 1430, 1320	73JHC947
H	Me	Ph	3100, 1475, 1440, 1330	73JHC947
H	Ph	H	1550	86JHC1531
H	<i>trans</i> -Styryl	H	1550	86JHC1531
H	(2,4-Cl <sub>2</sub> )C <sub>6</sub> H <sub>3</sub>	Ph	1600, 1570	86JHC1439
H	(2,4-Cl <sub>2</sub> )C <sub>6</sub> H <sub>3</sub>	(4-Br)C <sub>6</sub> H <sub>4</sub>	1610, 1575	86JHC1439
H	(2,4-Cl <sub>2</sub> )C <sub>6</sub> H <sub>3</sub>	(2,4-Cl <sub>2</sub> )C <sub>6</sub> H <sub>3</sub>	1610, 1570	86JHC1439
H	(2,4-Cl <sub>2</sub> )C <sub>6</sub> H <sub>3</sub>	(4-Cl)C <sub>6</sub> H <sub>4</sub>	1605, 1570	86JHC1439
H	CH <sub>2</sub> CO <sub>2</sub> Et	Ph	1560-1640	78JHC401

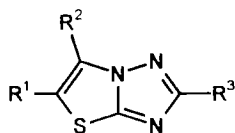
<sup>13</sup>C NMR data for condensed derivatives (thiazolo[3,2-*a*]benzimidazoles) have been reported (88CB977), but there does not seem to be a systematic investigation. <sup>15</sup>N NMR data are still lacking.

Mass spectral fragmentation schemes for thiazolo[3,2-*b*][1,2,4]triazoles have been given [87IJC(B)526].

#### D. BIOLOGICAL PROPERTIES

There have been numerous reports on the biological properties of thiazolo[3,2-*b*][1,2,4]triazoles (Table XVI).

TABLE XV  
UV DATA OF THIAZOLO[3,2-*b*][1,2,4]TRIAZOLES



R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	$\lambda_{\max}$ (lg $\epsilon$ ) in nm	Ref.
H	Me	Me	246 (3.91), 201 (3.80) <sup>a</sup>	71JOC10
H	Me	Ph	258 (4.36), 223 (4.10), 203 (4.43) <sup>a</sup>	71JOC10
H	Ph	Ph	262 (4.40), 198 (4.55) <sup>a</sup>	71JOC10
H	Ph	Me	270 (4.14), 227 (4.18), 202 (4.24) <sup>a</sup>	71JOC10
H	H	Me	241, 206 <sup>a</sup>	73JHC947
H	H	Ph	256 (4.33), 210 (4.20) <sup>a</sup>	73JHC947
-CH = CH - CH = CH-		Me	288 (3.50), 280 (3.45), 225 (4.43), 208 (4.18) <sup>a</sup>	73JHC947
-CH = CH - CH = CH-		Ph	296 (4.02), 284 (sh, 4.16), 267 (4.33), 240 (4.38), 213 (4.47) <sup>a</sup>	73JHC947
H	Me	Ph	258 (4.34), 233 (4.06), 203 (4.28) <sup>a</sup>	73JHC947
H	CH <sub>2</sub> CO <sub>2</sub> Et	Ph	268 <sup>b,c</sup>	78JHC401
CH <sub>2</sub> CO <sub>2</sub> Et	Me	Ph	294 (4.427), 240 (3.957), 210 (4.207) <sup>b</sup>	91AP49

<sup>a</sup> MeOH.

<sup>b</sup> EtOH.

<sup>c</sup> lg  $\epsilon$  seems to be misprinted in the original paper.

TABLE XVI  
BIOLOGICAL PROPERTIES OF THIAZOLO[3,2-*b*][1,2,4]TRIAZOLES

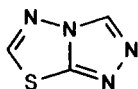
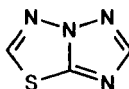
Biological function	Ref.
Preparation and pharmacological activity (anti-inflammatory, platelet aggregation inhibitory activity, toxicity)	94KFZ21
Antimicrobial agents	95MI3
Antiviral activity	94MI1
Vasodilatory properties	93FA707
2-Sulfonamide derivatives as herbicides	88EUP244098
Antibacterial properties of cephem derivatives	93MI3
Biological evaluation	91MI1
Reaction with chloro- and acetoxymethylcephem, activity	91MI2
Ulcer Inhibitors	90JAP(K)02/142797



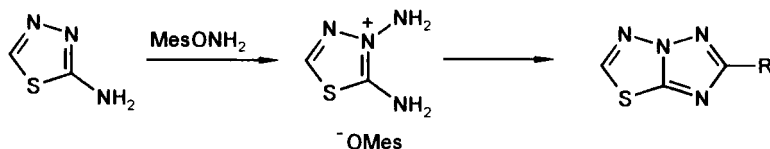
## IX. 1,2,4-Triazolo[5,1-*b*][1,3,4]thiadiazoles

### A. SYNTHESIS

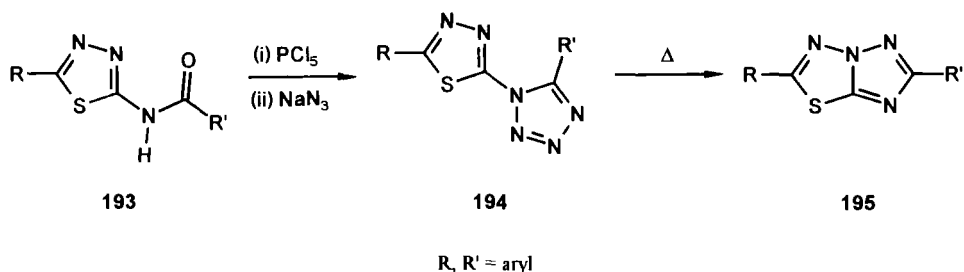
Whereas *s*-triazolo[3,4-*b*][1,3,4]thiadiazoles (1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazoles, **190**) are reported repeatedly, especially with respect to their fungicidal and bactericidal activity, the corresponding isomeric 1,2,4-triazolo[5,1-*b*][1,3,4]thiadiazol system **191** has been investigated far less intensively.

**190****191**

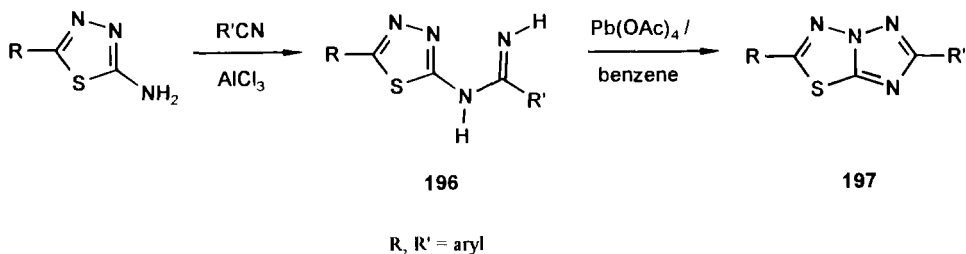
The synthetic approaches described thus far for **191** resemble quite closely those reported for similar heterocycles. The system has been prepared for the first time by Tamura and co-workers (79CPB2521). 2-Aminothiadiazoole can be aminated with *O*-mesitylsulfonylhydroxylamine, giving an *N*-3-aminated product that on treatment with acylating agents (benzoyl chloride, acetic acid anhydride, 200°C) yields the desired compounds (**192**, R = Me, Ph). Yields are low (15–26%).

**192**

The tetrazole procedure that has been proved to be of value in the thiazolo[3,2-*b*][1,2,4]triazole series (see Section VIII) has also been applied in this field. *N*-Acylated 2-aminothiadiazoles **193** on treatment with phosphorus pentachloride (120°C) and subsequently with sodium azide (aqueous acetone) yield tetrazoles **194**. Thermolysis in tetraline (160–180°C) gives the heterocycles **195** in moderate yields [85IJC(B)908; 90FA953].



The ring closure can also be effected by oxidizing reagents. 2-Aminothiadiazoles react with nitriles ( $\text{AlCl}_3$ ,  $\Delta$ ) to give amidines **196**. Whereas oxidizing agents such as nitrobenzene or potassium permanganate seem to be ineffective, cyclodehydrogenation (57JCS729, 66JOC260) with  $\text{Pb}(\text{OAc})_4$  results in the formation of triazolothiadiazoles [91IJC(B)435]. The formation of **197** can be explained through electrocyclization of a nitrene intermediate.

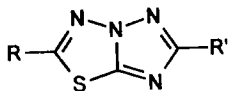


Yields seem to be generally better in comparison to the pyrolysis of tetrazoles. Earlier attempts (66JOC3528) seem to have been unsuccessful.

In Table XVII, some representative examples prepared by the various methods are given.

## B. SPECTROSCOPIC PROPERTIES

No systematic investigations of the spectroscopic properties have been reported. The  $^1\text{H}$  NMR spectra of 2-unsubstituted derivatives show a singlet at 8.63 ppm (**192**,  $\text{R} = \text{Me}$ ) and 8.65 ppm (**192**,  $\text{R} = \text{Ph}$ ) (79CPB2521). The IR spectra of 1,3,4-triazolo[5,1-*b*][1,3,4]thiadiazoles exhibit a  $\text{C}=\text{N}$  absorption at  $1610\text{--}1630\text{ cm}^{-1}$ . Structural and theoretical data are still lacking.

TABLE XVII  
 1,2,4-TRIAZOLO[5,1-*b*][1,3,4]THIADIAZOLES


R <sup>1</sup>	R <sup>2</sup>	mp (°C)	Yield (%)	Ref.
H	Me	117–118	15	79CPB2521
H	Ph	107	26	79CPB2521
Ph	Ph	168	36, <sup>a</sup> 50 <sup>b</sup>	85IJC(B)908, 91IJC(B)435
Ph	(4-Me)C <sub>6</sub> H <sub>4</sub>	190	53, <sup>a</sup> 53 <sup>b</sup>	85IJC(B)908, 91IJC(B)435
Ph	(4-NO <sub>2</sub> )C <sub>6</sub> H <sub>4</sub>	188	37, <sup>a</sup> 45 <sup>b</sup>	85IJC(B)908, 91IJC(B)435
(4-Me)C <sub>6</sub> H <sub>4</sub>	Ph	154	43, <sup>a</sup> 60 <sup>b</sup>	85IJC(B)908, 91IJC(B)435
(4-NO <sub>2</sub> )C <sub>6</sub> H <sub>4</sub>	Ph	225	50 <sup>a</sup>	85IJC(B)908

<sup>a</sup> Tetrazole procedure.<sup>b</sup> Oxidative cyclization of amidine.

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# Synthesis, Stereochemistry and Transformations of Cyclopentane-, Cyclohexane-, Cycloheptane-, and Cyclooctane-Fused 1,3-Oxazines, 1,3-Thiazines, and Pyrimidines

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## I. Introduction

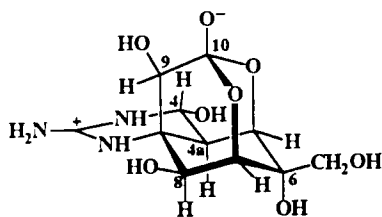
The continuing interest in the chemistry of the 1,3-oxazines and the related thiazines and pyrimidines may arise in part from their versatile synthetic applicability and their pharmacological usefulness. Although six-membered saturated or partially saturated 1,3-heterocycles and their derivatives fused with a benzene ring have been thoroughly studied since the beginning of the twentieth century, much less attention has been paid to their saturated counterparts, the related cycloalkane-fused bicyclic 1,3-heterocycles.

The extensive examinations of aromatic heterocycles, such as benzoxazines, benzothiazines, and quinazolines, and the corresponding oxo derivatives may also have been due to the fact that the starting materials of the syntheses of these hetero compounds, such as salicylic acid or anthranilic acid and their derivatives, have been industrial products since the end of the nineteenth century. In contrast, the starting materials for the stereospecific syntheses of the related cycloalkane-fused heterocycles can generally be prepared only with some difficulty and did not become available commercially until more recently [90MI1, 91MI1; 92ACH(129)107].

However, the strikingly rapid development of instrumental analysis, and especially the NMR and X-ray techniques, has provided the possibility of investigation of these stereostructures, which contain several chiral centers possessing much more complicated steric and conformational features than

the related aromatic systems. Investigation of these rather neglected ring systems seemed especially attractive with the arrival of the routine application of modern instrumental facilities, with regard to the fact that numerous natural products containing these structural moieties are known, many of them displaying interesting, and sometimes extreme, physiological activities.

Pioneering studies were made to determine the structure of tetrodotoxin **1**, one of the most toxic compounds among the low-molecular-weight poisons, found in the ovaries and liver of puffer fish, which is a highly esteemed delicacy in Japan. With a combination of the most versatile instrumental facilities, the complex perhydroquinazoline structure of **1** was established (65T2059) in the early 1960s.



**1**

Our present aim is to survey the chemistry and stereochemistry of cycloalkane-fused 1,3-oxazines, 1,3-thiazines, and pyrimidines. Only those derivatives are discussed in which the annelations involve  $sp^3$  carbon atoms, so that the possibility of *cis* and *trans* stereoisomers exists.

Partially and fully saturated derivatives of the following heterocyclic systems are discussed in this review:

Cyclopent[*d*][1,3]oxazine (**2**, X = O)

Cyclopenta[*d*][1,3]thiazine (**2**, X = S)

2*H*-3,1-Benzoxazine (**3**, X = O)

2*H*-3,1-Benzothiazine (**3**, X = S)

Cyclohept[*d*][1,3]oxazine (**4**, X = O)

Cyclohepta[*d*][1,3]thiazine (**4**, X = S)

2*H*-Cyclooct[*d*][1,3]oxazine (**5**, X = O)

2*H*-Cycloocta[*d*][1,3]thiazine (**5**, X = S)

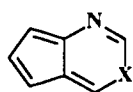
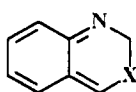
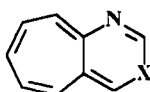
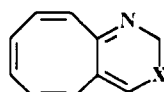
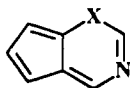
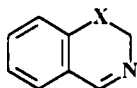
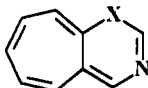
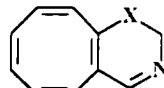
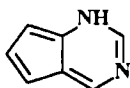
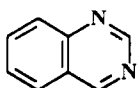
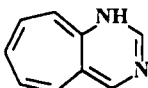
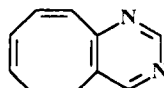
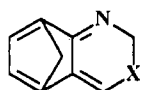
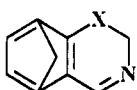
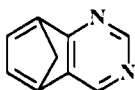
Cyclopent[*e*][1,3]oxazine (**6**, X = O)

Cyclopenta[*e*][1,3]thiazine (**6**, X = S)

2*H*-1,3-Benzoxazine (**7**, X = O)

2*H*-1,3-Benzothiazine (**7**, X = S)

Cyclohept[*e*][1,3]oxazine (**8**, X = O)

**2****3****4****5****6****7****8****9****10****11****12****13****14****15****16**

Cyclohepta[*e*][1,3]thiazine (**8**, X = S)

2*H*-Cyclooct[*e*][1,3]oxazine (**9**, X = O)

2*H*-Cycloocta[*e*][1,3]thiazine (**9**, X = S)

1*H*-Cyclopentapyrimidine (**10**)

Quinazoline (**11**)

1*H*-Cycloheptapyrimidine (**12**)

Cyclooctapyrimidine (**13**)

The synthesis and transformations of compounds **14–16**, the 5,8-methano derivatives of benzoxazines, benzothiazines, and quinazolines, are also discussed in several cases:

5,8-Methano-2*H*-3,1-benzoxazine (**14**, X = O)

5,8-Methano-2*H*-3,1-benzothiazine (**14**, X = S)

5,8-Methano-2*H*-1,3-benzoxazine (**15**, X = O)

5,8-Methano-2*H*-1,3-benzothiazine (**15**, X = S)

5,8-Methanoquinazoline (**16**)

In the reviewed articles, a quite inhomogeneous nomenclature is applied. Besides the correct IUPAC names, the nomenclature (83JCE95)

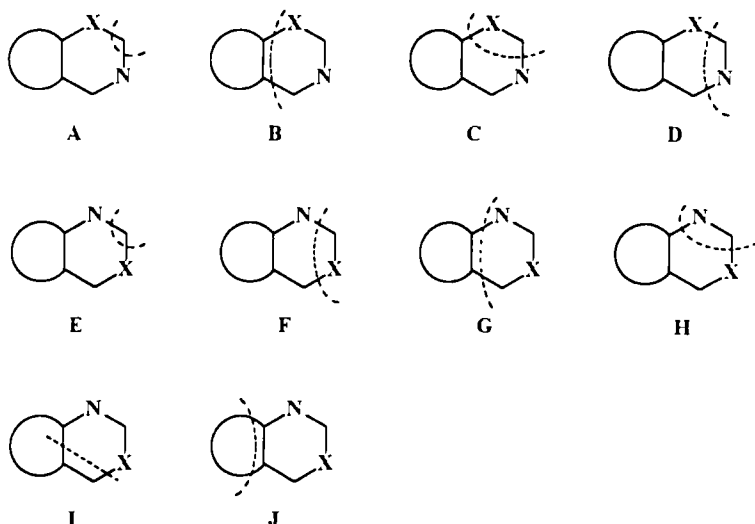


FIG. 1. The main ring syntheses of cycloalkane-fused 1,3-oxazine ( $X = O$ ), 1,3-thiazine ( $X = S$ ), and pyrimidine ( $X = N$ ) derivatives.

of trimethylene-, tetramethylene-, pentamethylene-, and hexamethylene-heterocycles are often used for the homologous series.

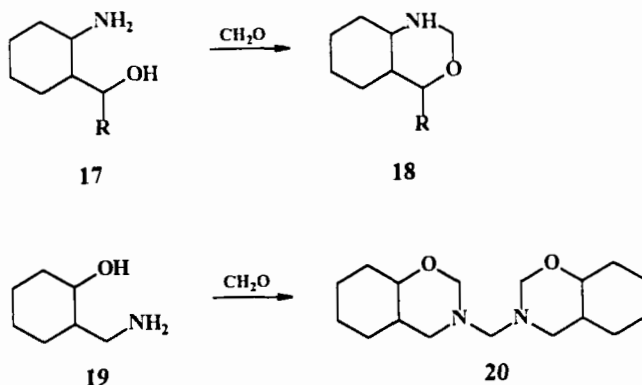
In the discussions, the syntheses, stereochemistry, and transformations of cycloalkane “*d*”-fused and “*e*”-fused systems are described in parallel; these correspond to 3,1-benzoxazines and 3,1-benzothiazines, and to 1,3-benzoxazines and 1,3-benzothiazines, respectively. The syntheses are frequently similar, but totally different methods are often used for the “*d*”-fused and “*e*”-fused heterocycles. The main syntheses (A–J) of the ring systems discussed in this review are given in Fig. 1.

## II. Methods of Preparation

### A. SYNTHESIS OF 1,3-OXAZINES

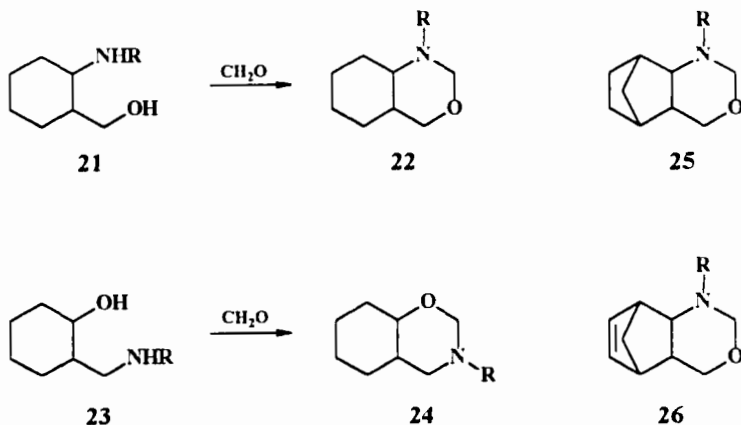
#### 1. Tetrahydro-1,3-oxazines

The simplest and most commonly used method for the synthesis of tetrahydro-1,3-oxazines is the ring closure of the corresponding 1,3-amino alcohols with oxo compounds [80H(14)1333]. The parent ring system is known merely in the case of 3,1-perhydrobenzoxazines **18** (*cis* or *trans*;  $R = H, Ph$ ); it was prepared from *cis*- and *trans*-2-hydroxymethyl-1-cyclohex-

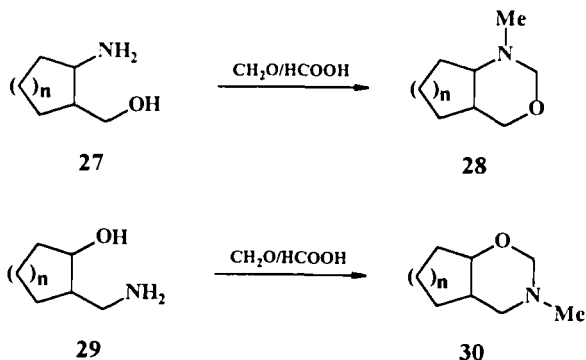


ylamine **17** with formaldehyde. In the reactions of the regioisomeric amino alcohols, *cis*- and *trans*-2-aminomethyl-1-cyclohexanols **19** and formaldehyde, the methylene-bridged bisoxazines **20** were formed (67JOC3300; 72MI1; 75ZOR612; 76MI1; 81MI1, 81MI2; 82MI2; 84ZOR2323).

The *N*-substituted 1,3-amino alcohols **21** and **23** react readily with formaldehyde, giving the corresponding 3,1- and 1,3-benzoxazines **22** and **24** ( $\text{R} = \text{Me}, \text{CH}_2\text{Ph}$ ) (84OMR527, 84T2053). In this way, the corresponding *diendo*- and *diexo*-norbornane- and norbornene-fused-1,3-oxazines **25** and **26** ( $\text{R} = \text{Me}, \text{CH}_2\text{Ph}$ ) were also prepared (85T5159). Preparation of the *cis* and *trans* isomers of **22** and their cyclopentane-fused analogs has been reported (94JOC5328), but without mention of the article published on the same compounds **22** (*cis* or *trans*;  $\text{R} = \text{CH}_2\text{Ph}$ ) 10 years earlier (84T2053).



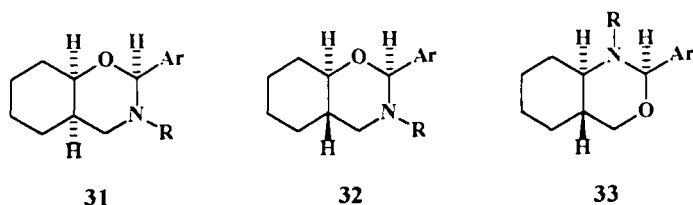
In the reactions of the *N*-unsubstituted parent amino alcohols **27** and **29** with a formaldehyde/formic acid mixture, ring closure and *N*-methylation



took place, resulting in *N*-methyl-substituted oxazines **28** and **30** in parallel [87ACSA(B)147].

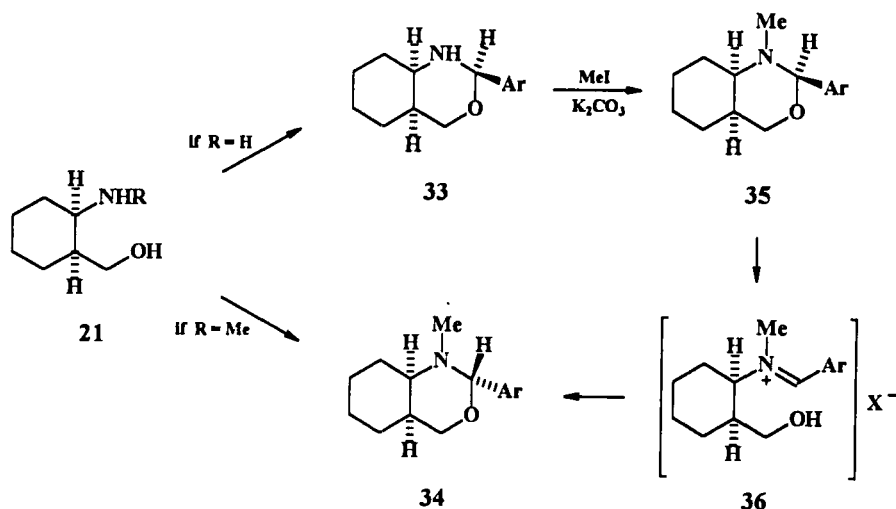
In the cases of *cis* and *trans* cyclohexane and *cis* cyclopentane derivatives, the ring closures gave products **28** and **30** in good yields, whereas, surprisingly, the *trans* cyclopentane amino alcohol failed to react. An explanation of the different reactivities of *cis* and *trans* cyclopentane derivatives is given in Section II,D.

The ring closures of *cis*- and *trans*-2-aminomethyl-1-cyclohexanols and *trans*-2-hydroxymethyl-1-cyclohexylamine with aromatic aldehydes are highly diastereoselective. After recrystallization of the reaction products, the presence of single diastereomers **31**–**33** was observed [72ACH(73)81; 80ACH(105)293, 80OMR204; 87JOC3821].

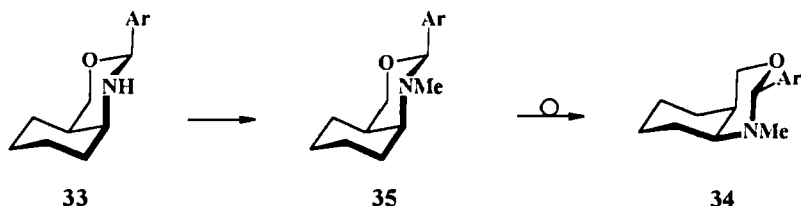


An interesting difference in the diastereoselectivity of the ring closure was found in the cyclizations of the *cis* amino alcohols **21** ( $\text{R} = \text{H}$ ,  $\text{Me}$ ) (84T3587). Depending on the *N*-substituent, C-2 epimers were isolated. The structures were determined by NMR and X-ray diffraction [82ACH(109)39; 84T3587].

In the methylation reaction of **33** with methyl iodide in the presence of potassium carbonate, the *N*-methyl derivative **35** was formed, which epimerized to **34** on standing in  $\text{CDCl}_3$  solution at room temperature. This epimerization can be rationalized in terms of the favored *N*-inside conformation **33** with an equatorial aryl group. On *N*-methylation, the



thermodynamically unfavored **35** (*N*-inside conformation, with an equatorial aryl group) was obtained, which epimerizes to the more stable **34** (*N*-outside conformation, with an equatorial aryl substituent) through an iminium salt **36**.

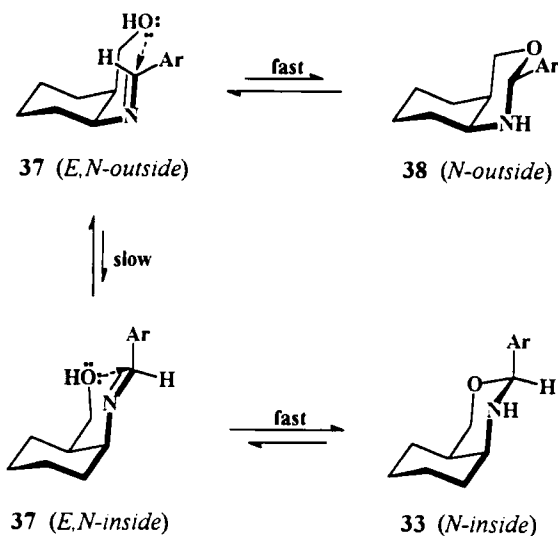


The foregoing facile epimerization, proceeding through a Schiff base intermediate, explains the high diastereoselectivity of the ring closures. Under the ring closure conditions, the predominant conformation of the product is determined by the configuration of C-2 under thermodynamic control; in the predominant conformation, the aryl group is *equatorial*.

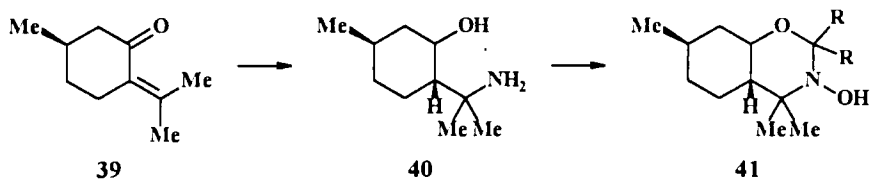
Similarly to the perhydrobenzoxazines **31**–**33**, the cyclopentane “*d*”- and “*e*”-fused derivatives and some of their *tert*-butyl-substituted derivatives have also been prepared [80LA122; 87JCS(P1)515, 87T1863; 94ACH(131)435].

The *N*-unsubstituted 2-aryltetrahydro-1,3-oxazines exhibit ring–chain tautomerism in solution. Depending on the steric and electronic characters of the substituents, the ring form and the open-chain Schiff base form occur in different ratios. For a more detailed discussion, see Section IV,A,4.

The cyclizations of *cis*- and *trans*-2-hydroxymethyl-1-cyclohexylamine and *cis*- and *trans*-2-aminomethyl-1-cyclohexanol with 4-nitrobenzaldehyde have been studied by means of  $^1\text{H}$  NMR spectroscopy in  $\text{CDCl}_3$  solution (90ACSA364; 91T2229). The time-dependent spectra confirmed that the reactions of all these amino alcohols proceeded via Schiff bases. With the exception of *cis*-2-hydroxymethyl-1-cyclohexylamine, the thermodynamically more stable perhydrobenzoxazine epimer is also the kinetically favored product. In the former case, from amino alcohol **21** ( $\text{R} = \text{H}$ ), the Schiff base **37** with *N*-outside predominant conformation is formed first; due to kinetic control, the less stable epimeric ring form **38** is obtained with *N*-outside predominant conformation. The thermodynamically controlled product **33** is formed subsequently, via the less stable open-chain form **37**, in a slow equilibration process (90ACSA364).



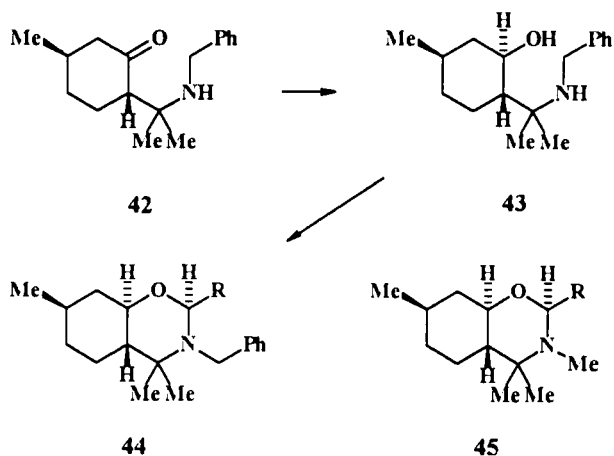
Two new types of optically active 1,3-oxazines (**41**) were synthesized by Rassat and Rey (74T265, 74T3315). The epimeric 1,3-amino alcohols **40**, prepared from (+)-pulegone **39** by Michael addition of ammonia and subsequent reduction, were cyclized with acetone, cyclohexanone, and 4-*tert*-





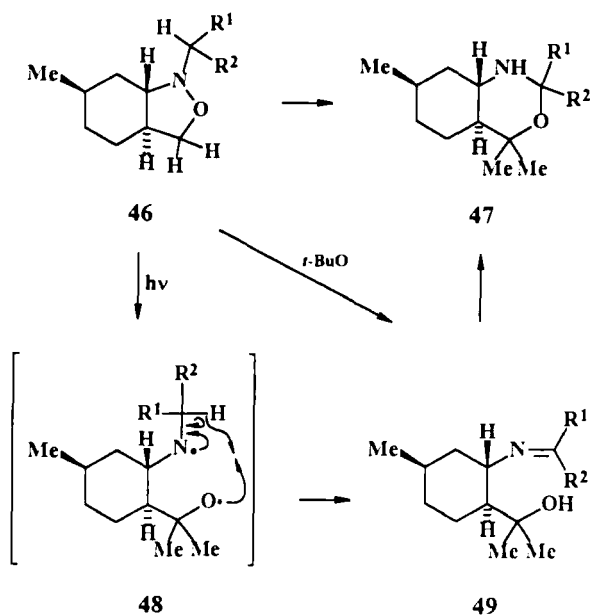
butylcyclohexanone and oxidized to the 4a*S*,7*R*,8a*R* and 4a*S*,7*R*,8a*S* epimeric benzoxazines **41** (74T3315).

Eliel and He prepared a new amino alcohol stereospecifically, from (+)-pulegone **39**. Michael addition of benzylamine took place stereospecifically, resulting in **42**, and subsequent sodium borohydride reduction gave the optically active amino alcohol **43**, which was cyclized with various aldehydes to **44** (R = COOMe, COMe, COEt, COiPr, CPh). The cyclizations were stereospecific except in the case of R = COOMe. *N*-Methyloxazines **45** were prepared from **43** by debenzylation, formylation, reduction, and ring closure. The octahydro-1,3-benzoxazines **44** and **45** were used as chiral auxiliaries in the highly enantioselective syntheses of  $\alpha$ -hydroxy acids (87T4979; 90JOC2114).

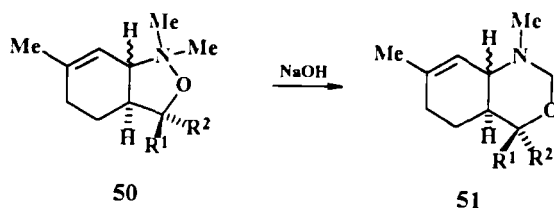


Further syntheses of tetrahydro-1,3-oxazines are individual processes based on the facile ring opening of isoxazolidines and recyclization to oxazines.

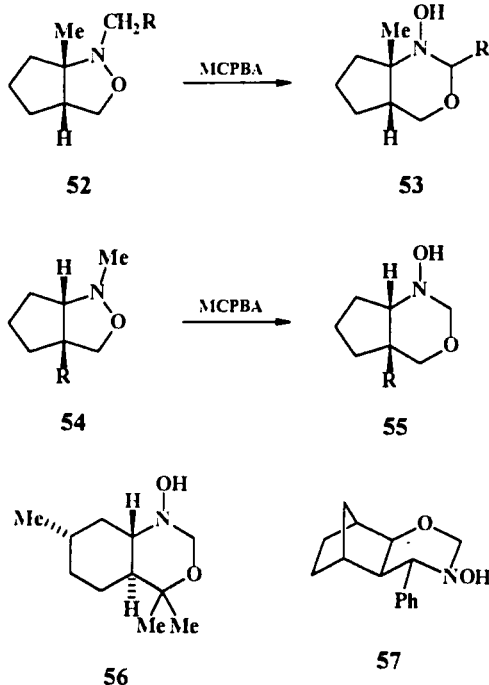
LeBel *et al.* described a photochemical ring transformation of isoxazolidines **46** (R<sup>1</sup> = R<sup>2</sup> = H; R<sup>1</sup> = R<sup>2</sup> = Me; R<sup>1</sup> = H, R<sup>2</sup> = Me) into the tetrahydrooxazines **47**. When **46** were heated with potassium *tert*-butoxide, the tetrahydrooxazines **47** were obtained in good yields (67JA3076). In the suggested mechanism via **46**, the Schiff base **49** is a common intermediate, which is also known from the thorough investigations on the ring-chain tautomerism.



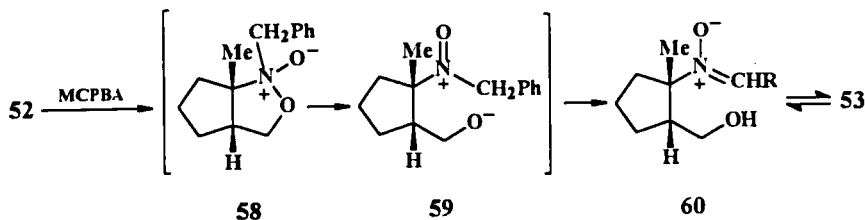
The preceding ring transformation was successfully applied to the methiodide of *N*-methylisoxazolidine **50**, which yielded *N*-methyloxazine **51** on the action of sodium hydroxide (79JOC953).



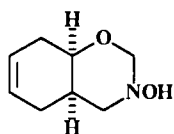
A simple oxidative ring enlargement of *N*-substituted oxazolidines **52** (R = H, Ph) to *N*-hydroxy-1,3-tetrahydrooxazines **53** has been described (64JOC1337; 65MI1; 66TL2173; 79JOC1819). **52** can be prepared by 1,3-dipolar cycloaddition of nitrones to olefins. The preceding reaction was used for the synthesis of cyclopentane-fused oxazines **55** (R = H, Me, Ph) and for the synthesis of 3,1-perhydrobenzoxazine **56** and norbornane-fused oxazine **57** (79JOC1819).



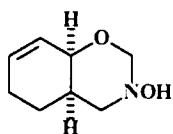
The presumed mechanism of the oxidative ring enlargement is shown for **52** ( $R = Ph$ ). The first step is the oxidation of the isoxazolidine to the unstable *N*-oxide **58**, which rearranges to the unstable dipolar **59**; this yields the methylene nitrene **60** by tautomerization. **60** gives oxazine **53**, through ring-chain tautomerization (79JOC1819).



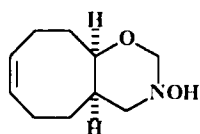
Bailey *et al.* used this oxidative rearrangement reaction for the synthesis of the regioisomeric "e"-fused 1,3-oxazine derivatives **61–63** (82JOC857).



61



62

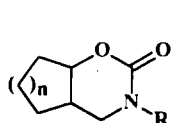


63

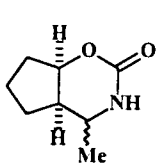
## 2. 2-Oxo, 2-Thioxo, and 2-Imino Derivatives of Tetrahydro-1,3-oxazines

a. *Tetrahydro-1,3-oxazin-2-ones*. For the preparation of tetrahydro-1,3-oxazin-2-ones, the most common method is the reaction of the appropriate 1,3-amino alcohol with a carbonic acid derivative. Compounds **64–75** were prepared by methods that are suitable for the preparation of both “*d*”- and “*e*”-fused derivatives.

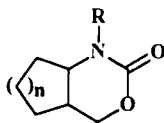
The following reagents have been used for the synthesis of **64–75**: urea (**64**, **66**, *cis* or *trans*;  $n = 1, 2, 3$ ;  $R = H, Me$ ) (73T981; 78IZV220; 83T1829); diethyl carbonate (**65**, methyl group  $\alpha$  and  $\beta$ ) (80LA122); ethyl chloroformate, followed by sodium methoxide (**64**, **66**, **67**, *cis* or *trans*;  $n = 1, 2$ ;  $R = Me$ ; **69**, aryl group  $\alpha$  and  $\beta$ ; **71**, **72**, *diendo* and *diexo*; **74** and **75**) [82H(19)1191;



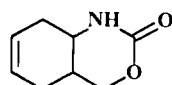
64



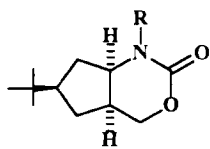
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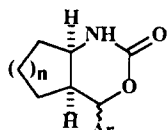
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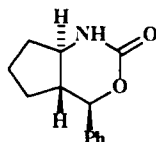
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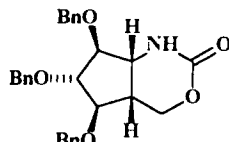
68



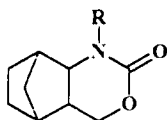
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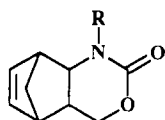
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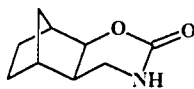
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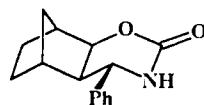
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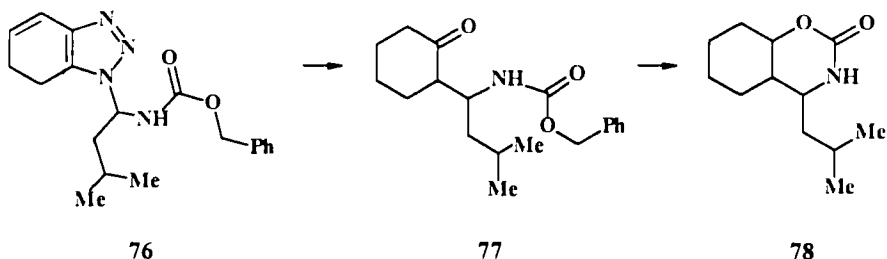
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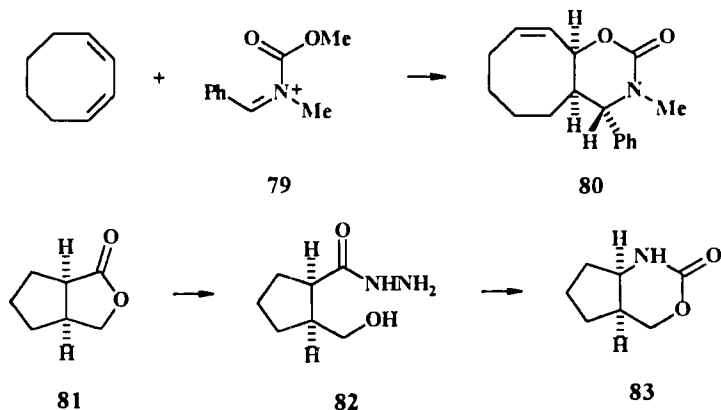
83JHC1181, 83T1829; 84CB3205, 84JHC1373; 85T1353; 86URP1203092; 89TL1253; 90MRC1045, 90T6859); phosgene (**68**, **70**) [86CB575; 94H(37)1687]; carbonyldiimidazole (**69**,  $n = 2$ ; aryl group  $\alpha$  and  $\beta$ ) (67JOC3300; 69FRP1579489, 69USP3452011); and phenyl chloroformate, in alkaline solution (**71**) (79HCA1990). The photolysis of azidoformates yielded *cis*- and *trans*-1,3-oxazin-2-ones of type **64** [87JCS(P1)1553]. The Pd(0)-catalyzed transformation of carbonates yielded *cis* carbamates of type **65** (94JOC1465).

From the readily available benzotriazole derivative **76**, Katritzky and Harris (90T987) prepared a diastereomeric mixture of the  $\beta$ -amino ketone **77** with the lithium enolate of cyclohexanone. In the reduction of **77** with lithium aluminium hydride, a reductive cyclization took place, resulting in the two diastereomeric oxazinones **78** in a ratio of 5:2. This cyclization can be regarded as a variation of the chloroformate cyclization under alkaline conditions.



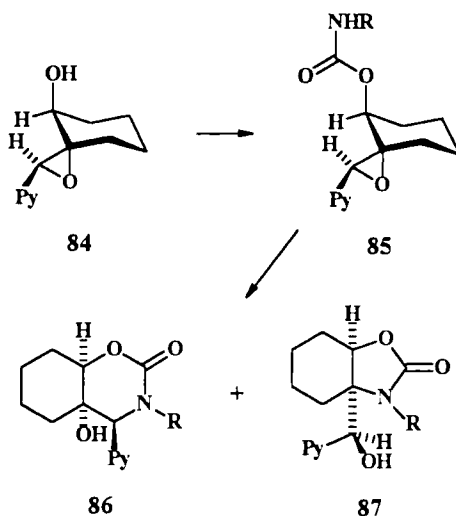
The following 1,3-oxazin-2-one syntheses have been applied individually.

Kahn and Chen (87TL1623) performed the regio- and stereospecific reaction of 1,3-cyclooctadiene and acyliminium derivative **79**, which resulted exclusively in compounds **80** in 37% yield after chromatographic purification. **79** was prepared by treatment of the *N*-methylimine of benzaldehyde with methyl chloroformate in the presence of titanium(IV) chloride.

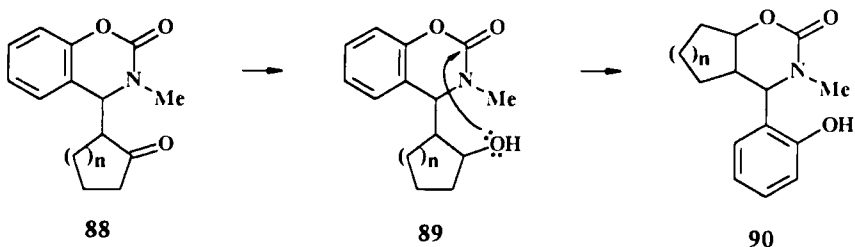


Cope and LeBel (60JA4656) prepared the *cis* lactone **81** from cyclopentane-*cis*-1,2-dicarboxylic anhydride and converted it to the hydrazide **82**. Curtius degradation of **82** gave the cyclic urethane **83**.

In the reaction of the conformationally restricted epoxy alcohol **84** and methyl or benzyl isocyanate, the epoxy carbamate **85** was formed. Cyclization of **85** in tetrahydrofuran in the presence of sodium hydride gave the oxazinone **86** in approximately 20% yield, and the oxazolidinone **87** (R = Me, CH<sub>2</sub>Ph) in 40–60% yield. The formation of the two products can be rationalized by different nucleophilic attacks on the urethane nitrogen. With increasing nucleophilicity of the nitrogen, the regioselectivity of the reaction is shifted toward the formation of **87** (92TL3009).



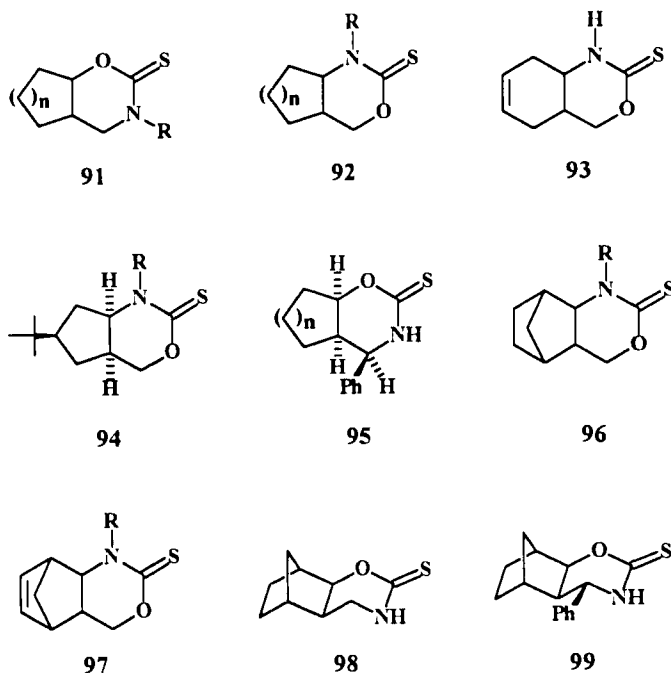
Bobowsky and Shavel found an interesting intramolecular reductive transacylation reaction, in which substituted cyclopent[*e*][1,3]oxazin-2-ones and 1,3-perhydrobenzoxazin-2-ones (**90**) were formed (80JHC277). In the reactions of 4-(2'-oxocycloalkyl)-3,4-dihydro-3-methyl-2*H*-1,3-benzoxazin-2-ones **88** and potassium borohydride, the 2'-hydroxycycloalkyl products **89** obtained underwent intramolecular transacylation reactions, resulting in the dihydro-1,3-oxazine derivatives **90**. In this way, the 4-(2'-oxocycloalkyl)



substituent was transformed into a 2-hydroxyphenyl group. In several cases, the intermediates **89** were also isolated. Neither the configurations of the products nor the stereochemistry of the reaction were investigated (80JHC277).

b. *Tetrahydro-1,3-oxazine-2-thiones*. The majority of the synthetic procedures used for the synthesis of 2-thioxotetrahydrooxazines apply the corresponding alicyclic 1,3-amino alcohols and thiophosgene or carbon disulfide for the cyclization.

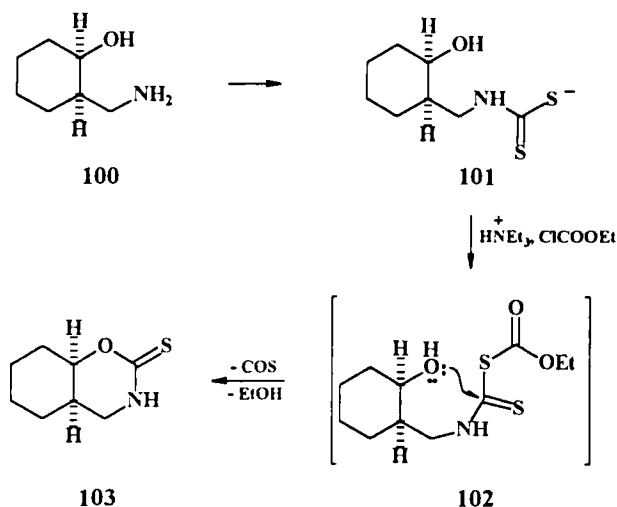
The following alicyclic 1,3-oxazine-2-thiones with the general structures **91–99** were synthesized by using thiophosgene or carbon disulfide via cyclization of the resulting thiocarbamate with lead(II) nitrate: **91, 92** (*cis* or *trans*;  $n = 1, 2$ ;  $R = H, Me$ ); **94, 96, 97** ( $R = H, Me$ ); **95** ( $n = 1, 2$ ); and **93, 98, 99** [82H(19)1191; 83JHC1181, 83T1829; 84JHC1373; 89KGS1668; 90MRC1045; 94H(37)1687]. Generally, the cyclizations occurred only in low yields (20–40%).



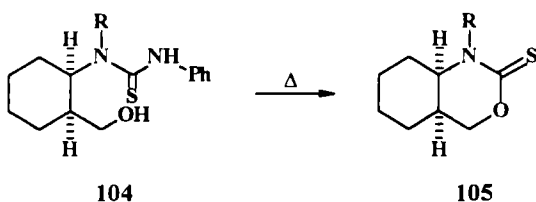
In contrast with tetrahydro-1,3-oxazine and tetrahydro-1,3-oxazin-4-one derivatives, the cyclization to 2-oxo and 2-thioxo derivatives was also successful with *trans*-1,2-disubstituted 1,3-difunctional systems such as *trans*-

2-aminomethyl-1-cyclopentanol, resulting in **91** (*trans*;  $n = 1$ ;  $R = H$ ;  $X = O, S$ ). For a discussion of the reactivity differences of the stereoisomers, see Section II,D.

To increase the yields of the ring closure reactions, a new method was developed that was successfully applied for the synthesis of alicyclic fused systems of both the parent oxazolidine-2-thione and tetrahydro-1,3-oxazine-2-thione (85S1149). As an example, the synthesis of 2-thioxoperhydro-1,3-benzoxazine **103** is described. The dithiocarbamate **101**, prepared from the amino alcohol **100**, carbon disulfide and triethylamine, was treated with ethyl chloroformate in the presence of triethylamine, to give the thioxo derivative **103** via the transition state **102** (85S1149). In this way, the fused-skeleton thioxooxazines (**91**,  $X = S$ , **92**) can be prepared with considerably higher yields (50–70%) than by the earlier methods (85S1149).



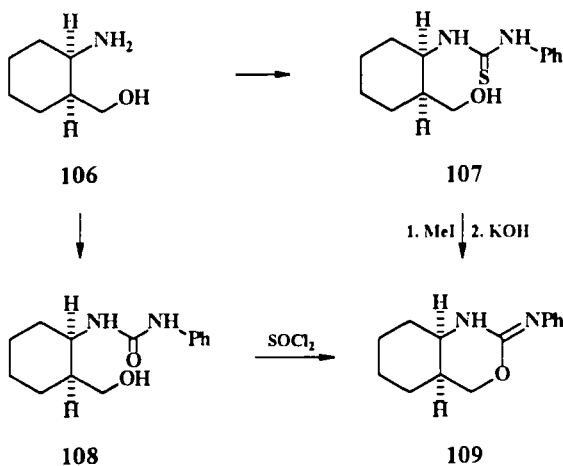
2-Thioxo derivatives **105** ( $R = H, Me$ ) were prepared through the thermal cyclization of thioureas **104**, which are readily available from the corresponding amino alcohols with phenyl isothiocyanate. The thermal cyclizations resulted in 1,3-oxazine-2-thiones by loss of aniline, but the yields were only moderate ( $R = H$ : 43%;  $R = Me$ : 31%) (88OPP73).



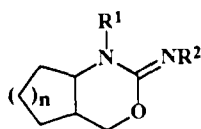


c. *2-Imino-substituted Tetrahydro-1,3-oxazines*. The preparation of these compounds is based in practice on two methods: transformation of the corresponding alicyclic 1,3-amino alcohol to a urea or thiourea adduct with isocyanates or isothiocyanates, and cyclization of the adduct to an iminooxazine in a straightforward process.

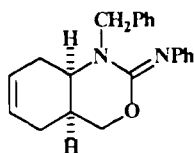
Further routes of cyclizations have been studied in parallel in the case of *cis*- and *trans*-2-hydroxymethyl-1-cyclohexylamine (**106**) (88OPP73). The preparation of thiourea or urea adducts **107** and **108** with phenyl isothiocyanate or phenyl isocyanate proceeds smoothly. The reaction of **107** with methyl iodide and subsequent alkali treatment, by elimination of methyl mercaptan, resulted in the iminooxazine **109** in high yields. The ring closures of both *cis* and *trans* thiourea adducts to 1,3-oxazines proceed with retention. Cyclodesulfuration of the adduct **107** by mercury(II) oxide or *N,N'*-dicyclohexylcarbodiimide resulted in the iminooxazine **109**, but the yield was low and the purification of the product was cumbersome. The ring closure of **108** with thionyl chloride led to the iminooxazine **109** in only moderate yield.



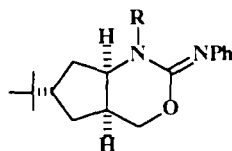
The best method (reaction with methyl iodide and subsequent alkali treatment of the thiourea formed) was used for the synthesis of the iminooxazines of types **110** (*cis* or *trans*;  $n = 1, 2$ ;  $R^1 = \text{H, Me, CH}_2\text{Ph}$ ;  $R^2 = \text{Me, Et, Ph}$ ) [87M503; 88ACH(125)193, 88OPP73]; **111** (88OPP73); **112** ( $R = \text{H, Me}$ ) [94H(37)1687]; and **113** (90T6859), and was also successfully applied for the synthesis of the corresponding methanobenzoxazines **114**, **115** (*diendo* and *diexo*;  $R = \text{H, Me, CH}_2\text{Ph}$ ) [87JCS(P2)599], **116** and **117** (87PHA448; 90MRC1045).



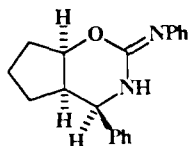
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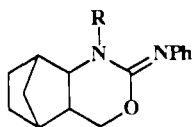
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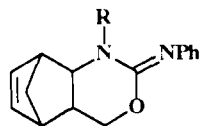
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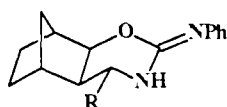
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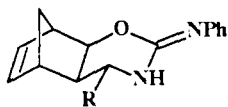
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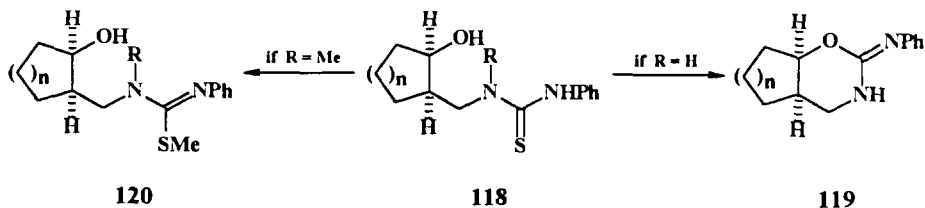


117

In the preceding cyclizations that resulted in compounds with “*d*”-fused rings, practically no differences were observed in the cyclizations of the *cis* and *trans* isomers; nor did the ring size exert an effect on the cyclizations.

Depending on the *cis* or *trans* configuration and the *N*-substituents, marked differences were found in the cyclizations of the corresponding ureas or thioureas to cyclopent[*e*][1,3]oxazines and octahydro-2*H*-1,3-benzoxazines (85T5981), when the cyclization occurs on an *sp*<sup>3</sup> carbon.

The reactions of the *cis* thiourea **118** ( $n = 1, 2$ ;  $R = H, Me$ ) with methyl iodide and subsequent alkali treatment, similar to the synthesis of **110–117**, afforded the unsubstituted oxazine derivatives **119**; only the attempted cyclization of the *N*-methyl analog failed, when the reaction furnished the isothiurea derivatives **120** ( $n = 1, 2$ ). Compounds **120** could not be



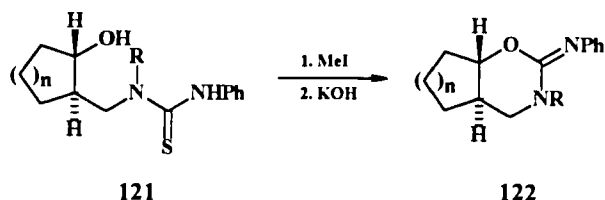
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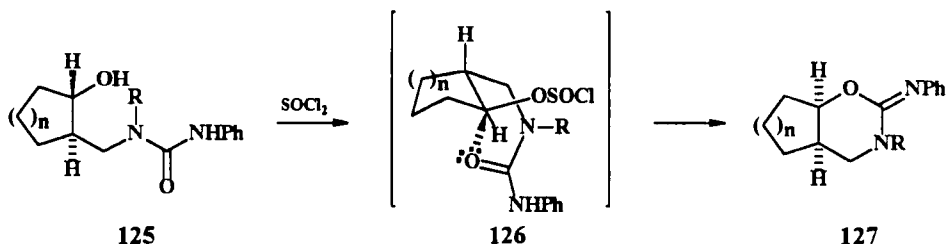
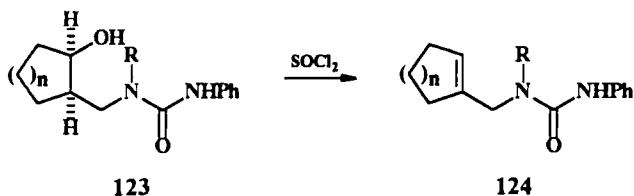
119

transformed to the oxazine even on heating with alkali or on treatment with mercury(II) chloride.

In the cyclization of the *trans* isomers **121** ( $n = 1, 2$ ;  $R = H, Me$ ), no difference was found in the reactions. The cyclizations proceeded in good yields (72–84%), resulting in **122** in all four cases ( $n = 1, 2$ ;  $R = H, Me$ ) (85T5981). The cyclizations to 1,3-oxazines took place with retention, which is in agreement with the suggested mechanism: formation of the thiuronium salt and subsequent nucleophilic attack of the oxygen on the partially positive carbon.

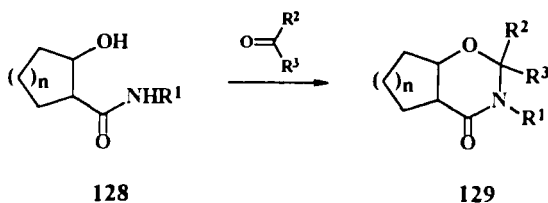


Depending on the configurations, the attempted cyclizations of ureas **123** and **125** with thionyl chloride yielded different products. Thionyl chloride treatment of the *cis* thiourea derivatives **123** ( $n = 1, 2$ ;  $R = H, Me$ ) resulted in products **124** by water elimination (85T5981). Similar treatment of the *trans* ureas **125** ( $n = 1, 2$ ;  $R = H, Me$ ) furnished the *cis* oxazines **127**. The reaction proceeded by an inversion mechanism, via the intermediate **126** (77MI1).



### 3. Tetrahydro-1,3-oxazin-4-ones and -4-Thiones

The ring closure of *cis*- and *trans*-2-hydroxy-1-cycloalkanecarboxamides **128** by reaction with aldehydes or ketones is the only conventional method for the preparation of the tetrahydro-1,3-oxazin-4-ones of general formula **129** [79ACH(101)61; 80MIP1; 85JHC377]. For these cyclizations, mainly aromatic and heteroaromatic aldehydes have been used, and the thermal ring closures were performed in the presence of a catalytic amount of acid. The cyclizations with ketones, such as acetone and cycloalkanones, were generally carried out at room temperature, in ethanol containing 1–2% of dry hydrogen chloride [79ACH(101)61].

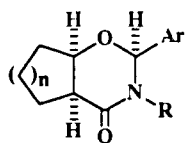
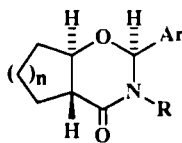


All the cyclization reactions for the formation of *cis* cyclopentane-, cyclohexane-, and cycloheptane-fused and *trans* cyclohexane- and cycloheptane-fused derivatives are smooth. In contrast, the cyclizations of *trans*-2-hydroxy-1-cyclopentanecarboxamide failed. The difference in reactivity of *cis* and *trans* isomers is discussed in Section II,D.

The observation that *trans*-2-hydroxy-1-cyclopentanecarboxamide does not react with aldehydes or ketones was used in the synthesis of stereohomogeneous *cis* cyclopentane-fused oxazinones and *cis*-2-aminomethyl-1-cyclopentanol derivatives. The cumbersome separation of the *cis*- and *trans*-2-hydroxy-1-cyclopentanecarboxamides can be avoided, because only the *cis* isomer forms the oxazinone ring (81S628; 83T1829).

The cyclization of *N*-substituted-2-hydroxy-1-carboxamides with aldehydes and ketones has been successfully performed only in the case of *N*-methyl derivatives. Under similar conditions, the unchanged starting material was recovered from the reactions of other *N*-substituted-carboxamides (*N*-substituent = Ph, CH<sub>2</sub>Ph or CH<sub>2</sub>CH<sub>2</sub>Ph) [84JCS(P1)2043].

The cyclizations of *N*-unsubstituted and *N*-methyl-2-hydroxy-1-cycloalkanecarboxamides with aldehydes or ketones took place stereospecifically. Only single diastereomers (**130**, **131**) were formed, with a new chiral center at C-2, the hydrogens attaining the same steric orientation as the annelation hydrogen next to the ring oxygen atom [84JCS(P1)2043]. The stereospeci-

**130****131**

ficity of the ring closure can be explained by the formation of the oxazinone ring in an equilibrium reaction, where the thermodynamically favored diastereomer with an equatorial 2-aryl substituent is obtained. For the *cis* isomers, therefore, the predominant *O-inside* conformation is the factor determining the diastereoselectivity of the ring closure.

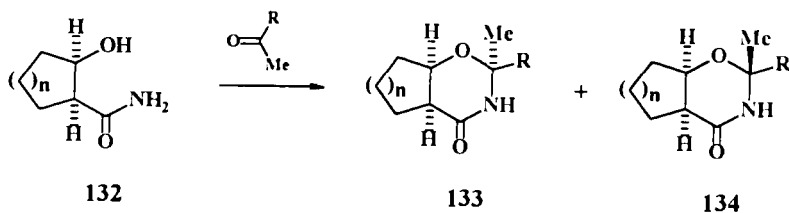
Diastereomeric 2,2-disubstituted-tetrahydro-1,3-oxazin-4-ones were synthesized from *cis*-2-hydroxy-1-cyclopentane- and -cyclohexanecarboxamides **132** by condensing them with nonsymmetric ketones, such as 2-butanone, 3-methyl-2-butanone, 3,3-dimethyl-2-butanone, or acetophenone (87T4565). The diastereomer product ratios are given in Table I.

The stereoselectivity of the reaction can be rationalized in terms of the relative stabilities of the products **133** and **134**. The stereoselectivity was more pronounced in the cyclohexane series. The stereoselectivity increases with increasing size of substituent R, and the reaction becomes a stereospecific process for the *tert*-butyl derivatives. The equatorial position of a bulkier substituent is preferred, and thus in the phenyl series the steric requirement of the phenyl group is smaller than that of the methyl group.

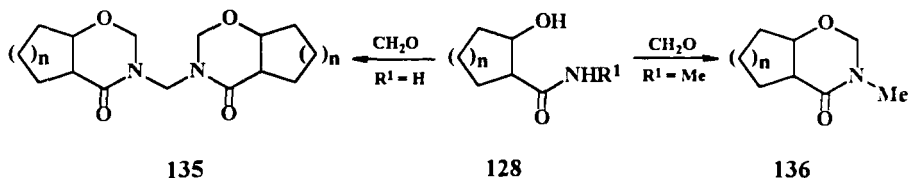
TABLE I  
DIASTEREOMER RATIOS<sup>a</sup> IN THE FORMATION OF  
TETRAHYDRO-1,3-OXAZIN-4-ONES **133** AND **134**

<i>n</i>	R	Ratio of <b>133</b> and <b>134</b>	
1	Et	67	33
2	Et	74	26
1	<i>i</i> Pr	78	22
2	<i>i</i> Pr	85	15
1	<i>t</i> Bu	100	0
2	<i>t</i> Bu	100	0
1	Ph	13	87
2	Ph	9	91

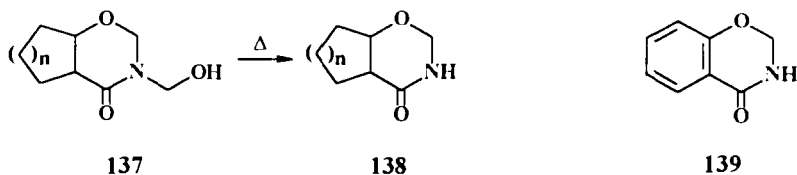
<sup>a</sup> Data from Fülöp *et al.* (87T4565).



The cyclization of **128** ( $R = H$ ) with formaldehyde gave the methylene-bridged bisoxazinones **135** [79ACH(101)61]. The corresponding *N*-methyl derivatives (**128**,  $R^1 = Me$ ) and formaldehyde yielded the *N*-methyloxazinones **136** [84JCS(P1)2043].

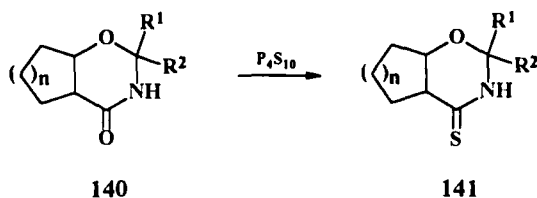


*cis*-2-Hydroxy-1-cyclopentane- and *cis*- and *trans*-2-hydroxy-1-cyclohexanecarboxamides and a formaldehyde/formic acid mixture furnished 3-hydroxymethyloxazines **137** in good yields (87TL115; 92T4963). Thermal decomposition of the 3-hydroxymethyl derivatives **137** (*cis*,  $n = 1, 2$ ; *trans*,  $n = 2$ ) led to the parent compounds **138** (*cis*,  $n = 1, 2$ ; *trans*,  $n = 2$ ).

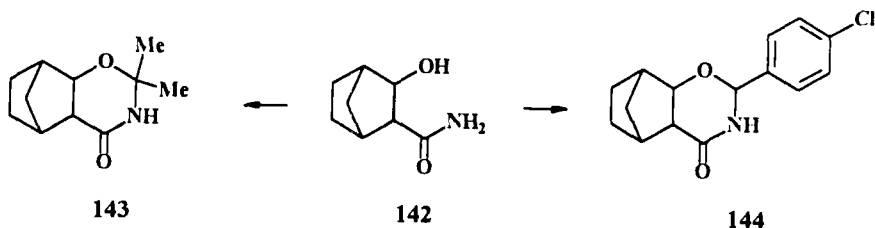


When the preceding reactions were carried out with salicylamide, the *N*-hydroxymethylbenzoxazinone was formed, which, after thermal decomposition, gave the previously unknown parent benzoxazinone **139** (92T4963).

The 4-oxo group of the oxazin-4-ones **140** was transformed with phosphorus(V) sulfide in pyridine to a 4-thioxo group, resulting in **141** (*cis*,  $n = 1, 2, 3$ ; *trans*,  $n = 2, 3$ ;  $R^1 = R^2 = Me$ ;  $R^1 = Ar$ ,  $R^2 = H$ ) in 30–85% yields (84PHA531).



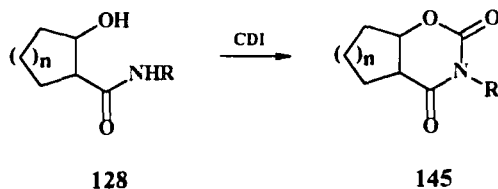
The cyclizations of *diendo*- or *diexo*-norbornane-3-hydroxy-2-carboxamides **142** with acetone result in **143**; similarly, **142** and *p*-chlorobenzaldehyde yield **144**, with *endo* and *exo* ring fusions, respectively (84CB3205).



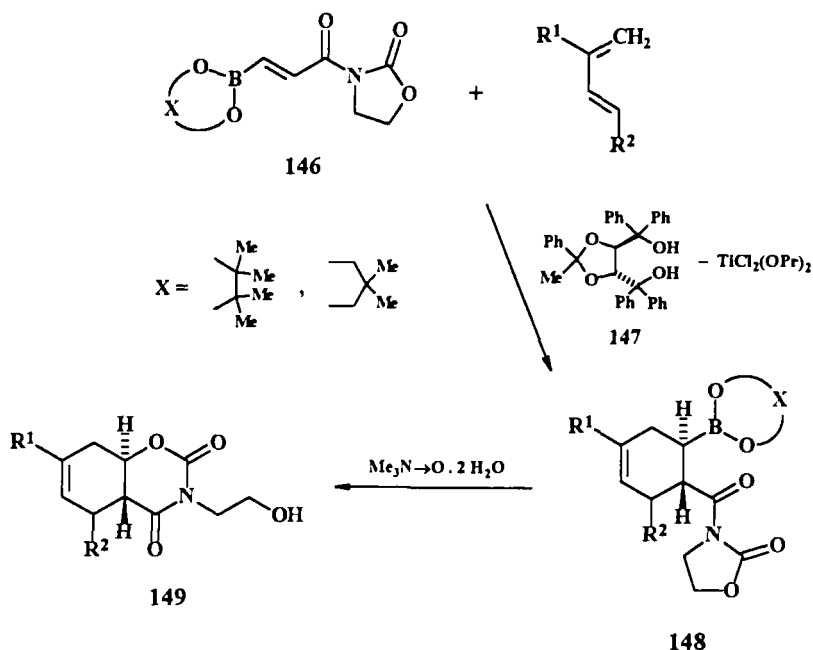
#### 4. 1,3-Oxazine-2,4-diones

Only two articles deal with the synthesis of saturated 1,3-benzoxazine-2,4-diones and the corresponding cyclopent[e][1,3]oxazines.

*N*-Substituted derivatives of *cis*-2-hydroxy-1-cyclopentanecarboxamide and *cis*- and *trans*-2-hydroxy-1-cyclohexanecarboxamide **128** were transformed with a large excess of 1,1'-carbonyldiimidazole to oxazinediones **145** (*cis*,  $n = 1, 2$ ; *trans*,  $n = 2$ ;  $R = \text{Me, Ph, CH}_2\text{Ph, CH}_2\text{CH}_2\text{Ph}$ ) in 40–90% yields. Derivatives with an unsubstituted nitrogen atom could not be isolated (85M857).



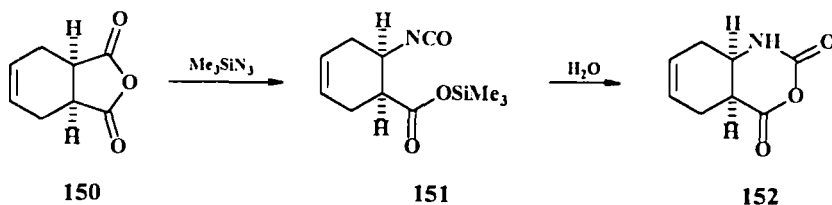
A catalytic asymmetric Diels–Alder reaction was developed by using 3-(3-borylpropenoyl)oxazolidin-2-ones **146**. In the reactions of butadiene, isoprene, or 2-methyl-1,3-pentadiene and **146**, in the presence of a chiral titanium catalyst **147**, the cyclohexene derivatives **148** were formed.



The adduct **148** was cyclized with trimethylamine *N*-oxide dihydrate to the benzoxazinediones **149** ( $R^1 = R^2 = H$  or Me;  $R^1 = Me, R^2 = H$ ). The reactions proceeded with high yields and high optical purity (92T5743; 94JPP06/65256).

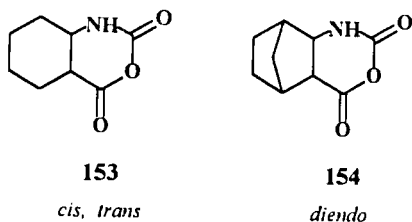
Although the 3,1-perhydrobenzoxazine-2,4-diones are the saturated analogs of the versatile synthon isatoic anhydride, few articles deal with the synthesis of these derivatives.

Kricheldorf has prepared the diones **152** (*cis*), **153** (*cis* and *trans*) and **154** (*diendo*) (73MI2). The synthesis is illustrated by the example of **152**.

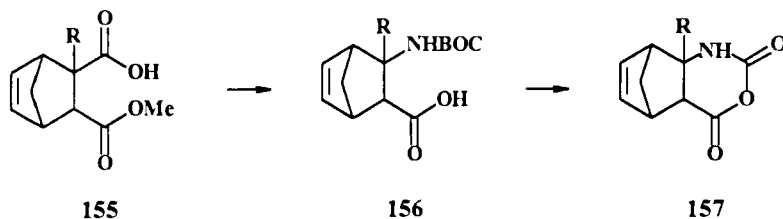


Anhydride **150** and trimethylsilyl azide in dioxane yielded an acyl azide, which by thermolysis, and Curtius degradation spontaneously furnished the isocyanate **151** (72CB3958; 74CB3533). Anhydride **152** was formed by silyl ester cleavage on hydrolysis [73MI2; 90JCS(P1)375].





Another method was developed for the synthesis of 5,8-methano-3,1-benzoxazine-2,4-diones **157**. The *N*-BOC amino acid **156** was prepared from the half ester **155** without purification of the intermediates. Thus, **155** was treated with ethyl chloroformate, and subsequently with sodium azide.



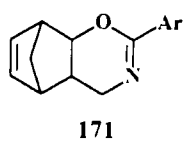
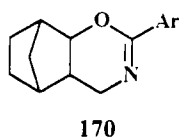
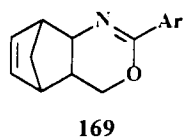
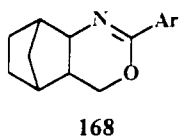
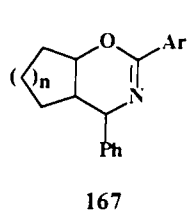
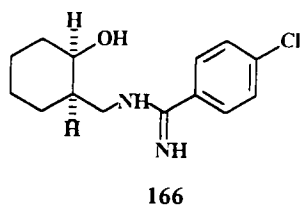
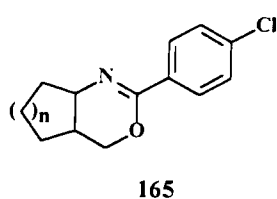
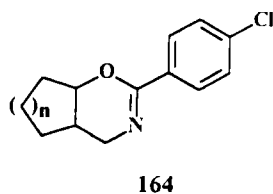
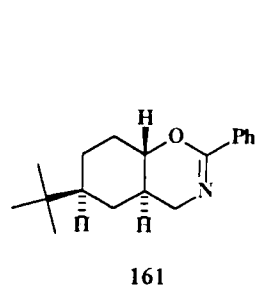
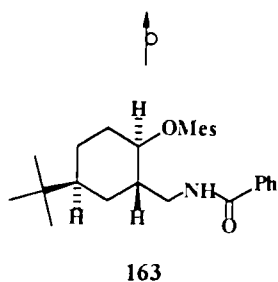
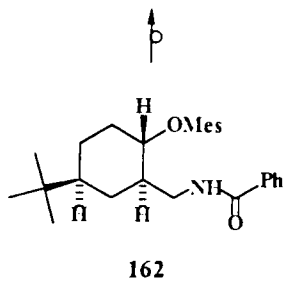
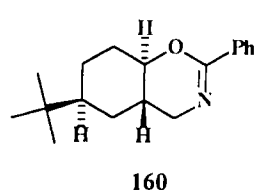
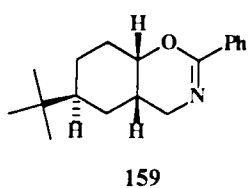
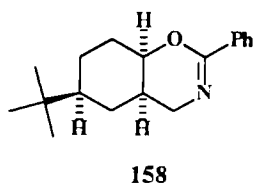
Curtius degradation of the acyl azide and subsequent transesterification with *tert*-butanol and hydrolysis resulted in the *N*-BOC amino acid **156**. Compound **156** was readily cyclized with thionyl chloride, resulting in anhydride **157** (*diendo*, R = H, Me; *diexo*, R = H) in one step. In the cyclization step, acid chlorides were formed first and thereafter an intramolecular cyclization took place with loss of hydrogen chloride (93BSB227, 93T1985).

### 5. Dihydro-1,3-oxazines

The simplest method for the preparation of dihydro-1,3-oxazines is the cyclization of the corresponding stereoisomeric 1,3-amino alcohol with imidates, or acylation of the amino alcohols and subsequent cyclization.

Pánková and Tichý prepared all four stereoisomeric 4-*tert*-butyl-2-aminomethyl-1-cyclohexanols and cyclized them with ethyl benzimidate to hexahydro-1,3-benzoxazines **158–161** (74CCC1447). From the *N*-acyl *O*-mesylate derivatives **162** and **163** on thermal cyclization or thionyl chloride treatment, ring closure occurred with inversion and resulted in **158** and **159** (74CCC1447).

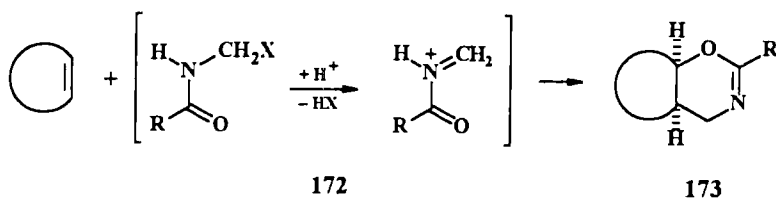
In the reactions of *cis*- and *trans*-2-aminomethyl-1-cyclohexanol or -1-cycloheptanol or *cis*- and *trans*-2-hydroxymethyl-1-cyclohexylamine or -1-cycloheptylamine with ethyl 4-chlorobenzimidate, the stereo- and regioisomeric derivatives and homologs **164** and **165** were prepared (79T799). The amidine intermediate **166** of the benzimidate ring closure was also



isolated, and the mechanism of the reaction was discussed. The thionyl chloride cyclization of the benzoyl derivatives of *trans*-2-aminomethyl-1-cyclohexanol took place with inversion, resulting in the *cis*-dihydrooxazine derivative **164** ( $n = 2$ ) (77ZOR327; 79T799).

Further stereoisomeric derivatives of the 1,3-oxazines **167** ( $n = 1, 2$ ; Ph  $\alpha$  or  $\beta$ ) (82MI1; 90T6859), and of **168–171** (*diendo* and *diexo*) (83JHC1181; 84JHC1373; 87MRC584) and several of their 4-aryl-substituted derivatives, were also prepared by ring closure with imidates (90MRC1045).

The most versatile method for the preparation of *cis*-hexahydro-1,3-benzoxazines and the related cycloalkane “*e*”-fused dihydrooxazines is amidoalkylation via 1,4-polar cycloaddition of the amidomethyl ion **172** to a cycloalkene. The addition is stereospecifically *cis*, and in accordance with the Markownikov rule is generally regiospecific.



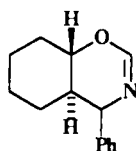
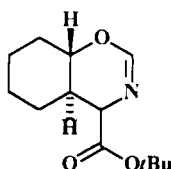
This reaction can be applied to different reagent combinations. The reagents most often used are carboxamides and formaldehyde or nitriles and formaldehyde (67FRP1478076; 71ITP886285, 71S92; 93T3907). The cycloalkane[*e*]oxazines **173** prepared by this method are listed in Table II.

TABLE II  
DIHYDRO-1,3-OXAZINES **173a–o** PREPARED

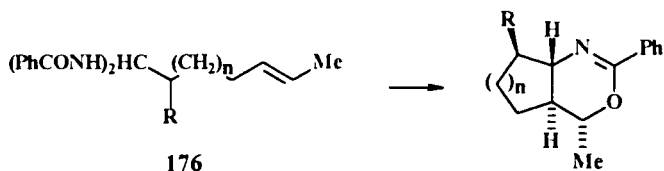
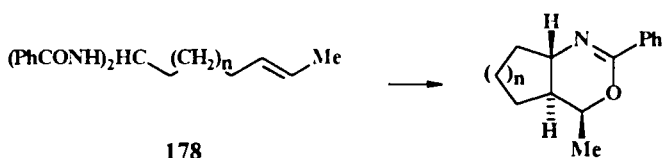
Compound	<i>n</i>	R	Ref.
<b>173a</b>	2	H	93T3907
<b>173b</b>	1	Me	85ACH(118)139
<b>173c</b>	2	Me	71S92; 85ACH(118)139
<b>173d</b>	4	Me	85ACH(118)139
<b>173e</b>	1	Ph	85ACH(118)139
<b>173f</b>	2	Ph	66AG913, 66LA(697)171; 69AG576; 71S92; 93MRC615, 93T3907; 94JOC3530, 94TL3231
<b>173g</b>	3	Ph	85ACH(118)139
<b>173h</b>	4	Ph	85ACH(118)139
<b>173i</b>	8	Ph	85ACH(118)139
<b>173j</b>	2	C <sub>6</sub> H <sub>4</sub> Cl( <i>p</i> )	85ACH(118)139
<b>173k</b>	2	CH=CH <sub>2</sub>	66AG913, 66LA(697)171; 93MRC615, 93T3907
<b>173l</b>	2	CH(Et)Ph	70CB3242
<b>173m</b>	1	OE <sub>t</sub>	70CB3242
<b>173n</b>	1	NMe <sub>2</sub>	70CB3242
<b>173o</b>	2	1-Adamantyl	84CPB1433

Conjugated dienes such as cyclopentadiene, 1,3-cyclohexadiene, and 1,3-cyclooctadiene result in the corresponding dihydrooxazine with a double bond in the alicyclic ring (70CB3242). Cycloaddition of the amidomethyl cation to norbornene takes place with *exo* selectivity (70CB3242).

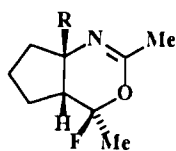
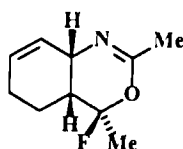
Schöllkopf *et al.* reacted lithiated isocyanides with epoxides to obtain 3-hydroxyalkyl isocyanides. The reaction was also performed with cyclohexene oxide, and the hydroxyisocyanate formed was cyclized to oxazines with copper(I) oxide, resulting in a diastereomeric mixture of **174** and **175** (76LA2105; 86AG755). Irradiation of aliphatic dieneamides yielded a variety of dihydrooxazines of type **167** (88T1959).

**174****175**

A basically new type of synthesis of dihydrooxazines was applied for the preparation of **177** and **179** (86JOC3248). Boron trifluoride catalyzed the intramolecular [4+2] cycloaddition of the *N*-acyliminium compounds derived from **176** and **178**, resulting stereospecifically in the *trans*-fused cyclopent[*d*][1,3]oxazines and partly saturated 3,1-benzoxazines **177** and **179**, respectively. The steric orientation of the 4-methyl substituent of the product is controlled by the *Z* and *E* geometry of the starting bisamides **176** and **178** (86JOC3248).

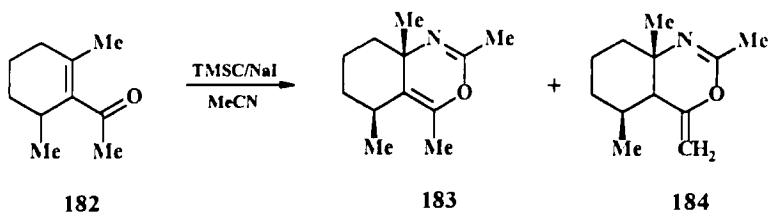
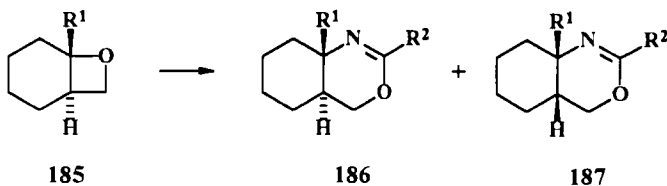
**177****179**

New types of fluorinated cyclopent[*d*]-3,1-oxazines and tetrahydro-4*H*-3,1-benzoxazines **180** and **181** were prepared (88IZV132; 89TL-1987; 91IZV1130, 91T5577). Cyclopentene, 1-methylcyclopentene, or 1,3-cyclohexadiene was reacted with a mixture of acetyl boron trifluoride and acetonitrile, resulting in the oxazines **180** and **181** regio- and stereospecifically via acylamidation.

**180****181**

When the enone **182** was heated with trimethylsilyl chloride (TMSCl) and sodium iodide in acetonitrile, a mixture of the 3,1-benzoxazines **183** and **184** in a ratio of 1 : 5 was formed stereospecifically. The  $\alpha,\beta$ -unsaturated ketones in TMSCl/NaI first gave  $\beta$ -iodoketones; thereafter a tertiary carbocation was formed, and subsequent acetonitrile addition resulted in the oxazines **183** and **184** (89TL4741).

The ring opening of the oxetanes **185** in sulfuric acid, in the presence of acetonitrile or benzonitrile, resulted in a mixture of the *cis*- and *trans*-3,1-benzoxazines **186** and **187** ( $R^1 = \text{Et, Pr, Ph}$ ;  $R^2 = \text{Me, Ph}$ ). The ratio of the diastereomers formed was not reported (82ZOR178, 82ZOR181). The

**182****183****184****185****186****187**

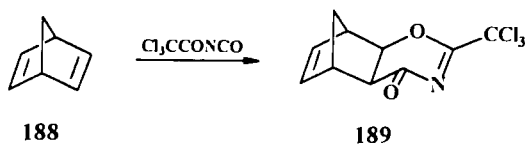
$R^1 = \text{Et, Pr, Ph}; R^2 = \text{Me, Ph}$

stereoisomers of 2-aryl-substituted derivatives were separated by fractional crystallization, while the 2-methyl derivatives were separated in the form of the corresponding amides after their hydrolysis (82ZOR181).

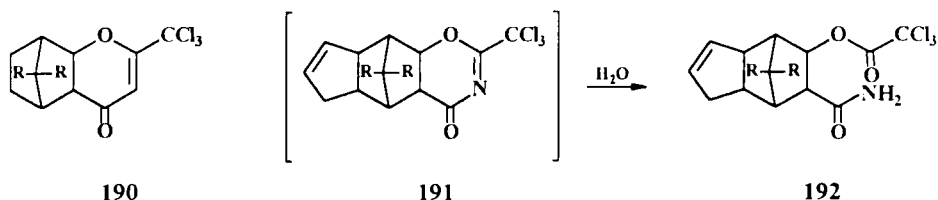
### 6. Dihydro-1,3-oxazin-4-ones

Two types of dihydro-1,3-oxazinones are relevant to the discussed topic: the "e"-fused hexahydro-2*H*-1,3-benzoxazin-4-ones and their homologs, and the "d"-fused hexahydro-2*H*-3,1-benzoxazin-4-ones and their homologs. For the synthesis of these derivatives, just two methods are known.

Nucleophilic olefins react readily with trichloroacetyl isocyanate to give 1,3-oxazin-4-ones. In this way, norbornadiene **188** yields the 5,8-methano-2*H*-1,3-benzoxazin-4-one **189** (69JOC633). A similar 1,4-addition starting

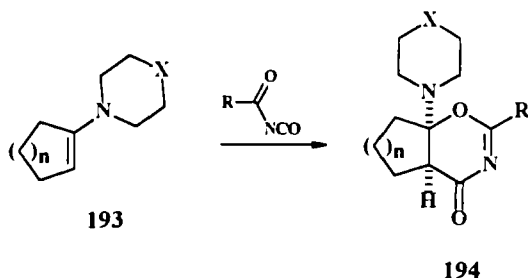


from norbornene and cyclopentadiene resulted in oxazinones **190** and **191**, respectively [69JOC633, 69LA(722)142; 74JA6492]. Compound **191** was found to be extremely unstable: Even atmospheric moisture converted it to the amido ester **192** (69JOC633).

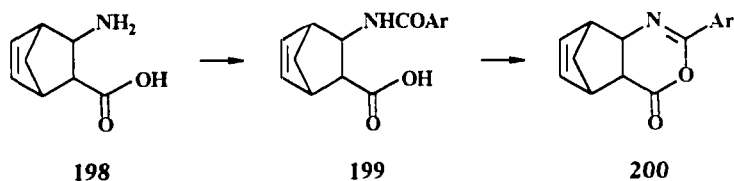
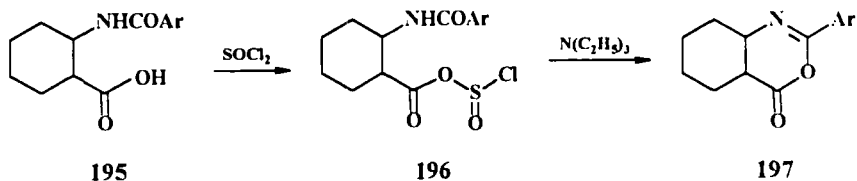


Arbuzov and Zobova found that aliphatic and aromatic acyl isocyanates react readily with cyclopentenes and cyclohexenes when the C=C bond is activated by a nucleophilic substituent, such as the piperidinyl or morpholinyl group (74S461; 82S433). Thus, **193** ( $n = 1, 2$ ; X = CH<sub>2</sub>, O) were reacted with benzoyl isocyanate and trichloroacetyl isocyanate, resulting in the oxazinones **194** ( $n = 1, 2$ ; X = CH<sub>2</sub>, O; R = Ph, CCl<sub>3</sub>) (72IZV2086; 93JOC414).

The 1,4-cycloadditions gave the *diexo* adducts stereoselectively from norbornene, and *cis* adducts in the cycloalkene series.



Nohira *et al.* treated *N*-acylamino acids **195** with thionyl chloride; mixed anhydrides **196** were formed below 30°C. The latter compounds gave the first type of hexahydro-2*H*-3,1-benzoxazin-4-one **197** on triethylamine treatment [77H(7)301]. This reaction was also performed with *diexo*- and *diendo*-substituted  $\beta$ -amino acids; **198** yielded the 5,8-methano-2*H*-3,1-benzoxazin-4-ones **199** via the acyl derivatives **200** (84S345, 84T2385). Further homologs were also prepared by the dehydration of *N*-acylamino acid derivatives (85MI1; 88MI3).

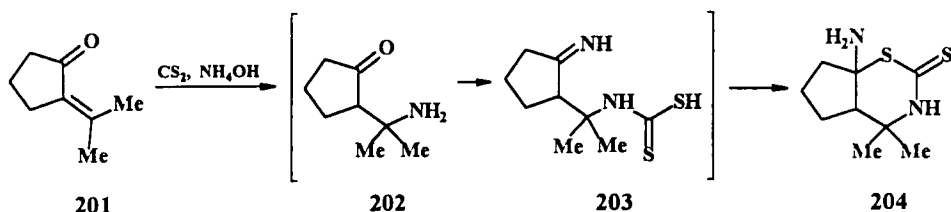


## B. SYNTHESIS OF 1,3-THIAZINES

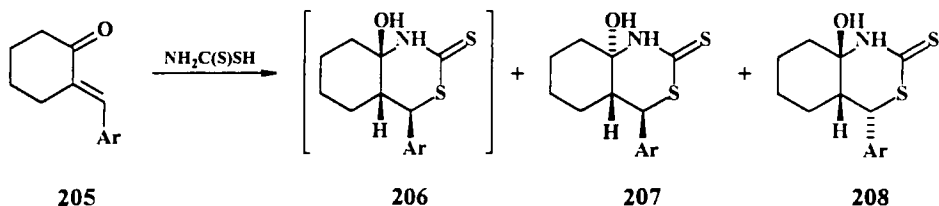
In comparison with the 1,3-oxazines, much less attention has been paid to the synthesis of cycloalkane-fused 1,3-thiazines. Only a few 2-thio-, 2-imino-, and 2,4-dioxotetrahydro derivatives are known. The most versatile method for the synthesis of the dihydro derivatives is cycloaddition.

1. *Tetrahydro-1,3-thiazines*

In the reaction of 2-isopropylidene-1-cyclopentanone **201** with carbon disulfide and ammonia, the perhydrocyclopenta[*e*][1,3]thiazine-2-thione derivative **204** was formed. The probable intermediates of the reaction are the Michael adduct **202** and the 2-imino-1-cyclopentanedithiocarbamic acid derivative **203**. Under similar conditions, the related alkylidene derivatives gave the corresponding 3-substituted-2-imino-1-cyclopentanedithiocarbamic acid derivatives. Further substituted derivatives and homologs of **204** were also synthesized (74AKZ319), but the stereochemistry of these compounds was not investigated [73JCS(P1)1009].



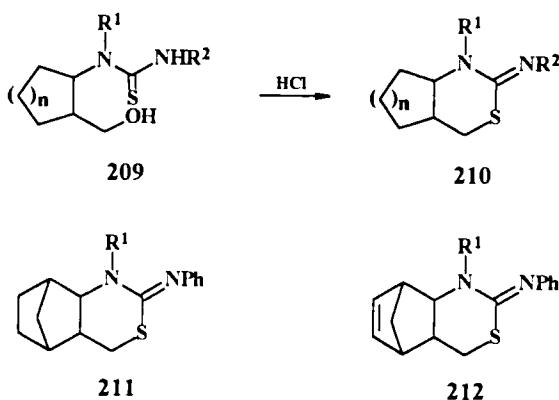
Perjési *et al.* thoroughly investigated the reactions of 2-arylidene-1-cyclohexanones with dithiocarbamic acid, which gave three of the four possible diastereomeric perhydro-3,1-benzothiazine-2-thiones **206–208**. Isomer **206** was found to be an unstable, kinetically controlled product, which readily isomerizes to **207** (87TL571). The isomer ratio depended greatly on the hydrochloric acid catalyst used in the reaction. Under less acidic conditions, the proportion of **208** was higher, whereas under more acidic conditions the formation of **207** was preferred (89CB651). In methanolic or ethanolic solution, a facile acid-catalyzed *O*-alkylation of the products **207** and **208** was observed (93CB1951). In the similar reactions of the corresponding 2-arylidene-1-cyclopentanones, only one isomer of the cyclopenta[*d*]-fused analog of isomer **208** was formed [87AX(C)324].



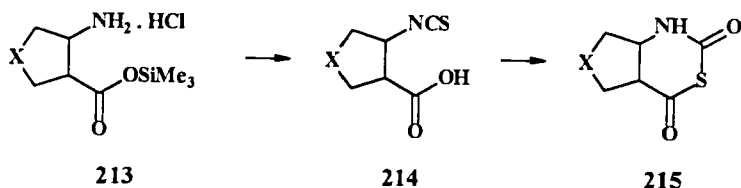
The thiocarbamide adducts **209**, readily obtained from the corresponding 1,3-amino alcohols, can be cyclized to “*d*”-fused 2-iminotetrahydrothiazines



**210** (*cis* or *trans*;  $n = 1, 2$ ;  $R^1 = \text{H, Me, CH}_2\text{Ph}$ ;  $R^2 = \text{Me, Et, Ph}$ ) under acidic conditions [87M503; 88ACH(125)193, 88OPP73; 94H(37)1687]. The cyclization can be performed with either aqueous or ethanolic hydrogen chloride, but the latter gives higher yields (88OPP73). The preceding cyclization was also applied for the synthesis of norbornane- and norbornene-fused thiazines **211** and **212** [87JCS(P2)599]. Under similar conditions, the attempted cyclization of the regioisomeric amino alcohols that would give “*e*”-fusion to thiazines proved unsuccessful (87PHA448).

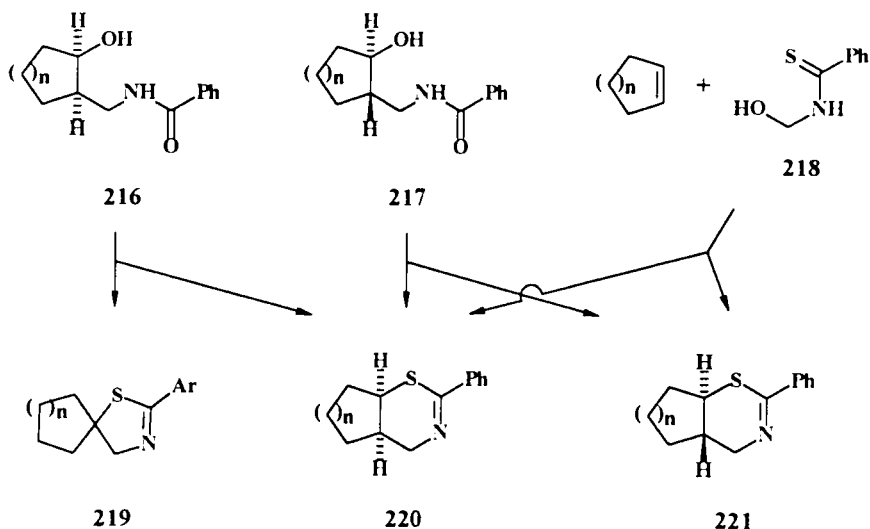


Alicyclic 2-isocyanato-1-carboxylic acids **214** synthesized from alicyclic trimethylsilyl 2-amino-1-carboxylates **213** were cyclized to the unstable 2-thioxoperhydro-1,3-oxazin-4-ones, which isomerize to the thermodynamically more stable perhydro-1,3-thiazine-2,4-diones **215** (*cis*,  $X = \text{CH}_2 - \text{CH}_2$ ,  $\text{CH} = \text{CH}$ ; *trans*,  $X = \text{CH}_2 - \text{CH}_2$ ) (74MI2).



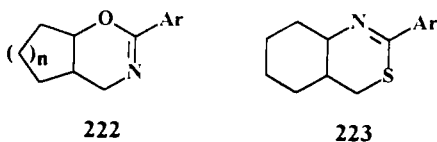
## 2. Dihydro-1,3-thiazines

Interesting observations were made on the cyclization reactions of *N*-benzoyl-*cis*- and *trans*-2-aminomethyl-1-cyclanols **216** and **217** with  $\text{P}_4\text{S}_{10}$ . From the *cis* isomers the spiro derivatives **219** were the main products, while the *cis* thiazines **220** were the minor products. In the cyclization of



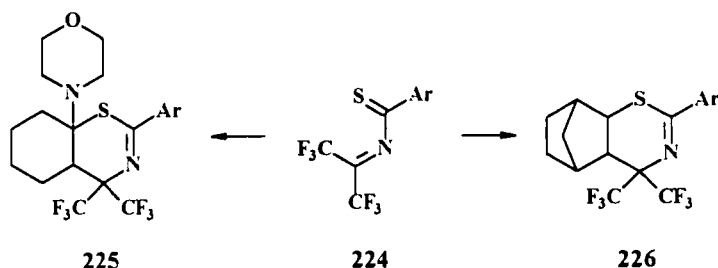
the *trans* isomers, the *cis*-thiazines **220** were the main products and the *trans* isomers **221** the minor products. The cycloaddition of hydroxymethylthiobenzamide to cycloalkenes gave the *cis* thiazine **220** besides 5–20% of the *trans* thiazine **221**. The latter is a noteworthy observation, since the thioamidoalkylation is described as a regio- and stereospecific process [72ITP934211; 73JCS(P1)771]. These investigations were performed with 5-, 6-, 7-, and 8-membered alicycles, but no significant trend could be observed in the variation of the diastereomer ratio with the ring size [85ACH(118)37].

When the *cis*-fused dihydrooxazines **222** were reacted with  $\text{P}_4\text{S}_{10}$ , oxygen  $\rightarrow$  sulfur exchange took place with inversion, resulting in the corresponding *trans* thiazines **221** ( $n = 1-4, 8$ ). In the regioisomeric *cis*- and *trans*-hexahydro-3,1-benzoxazines, on reaction with  $\text{P}_4\text{S}_{10}$  an  $\text{O} \rightarrow \text{S}$  exchange took place with retention of the configuration, resulting in the *cis* and *trans* thiazines **223** [85ACH(118)37].

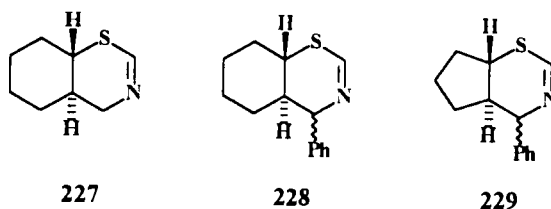


1,3-Thiazetes are formed on the thermolysis of 4-aryl-2,2,6,6-tetra(trifluoromethyl)-6*H*-1,3,5-oxathiazine. These thiazines are in thermally mobile equilibrium with (perfluoroisopropylidene)thiocarboxamide **224**. The latter

diene gave a new possibility for the synthesis of fluorinated dihydrothiazines. The addition of **224** to cycloalkenes containing an activated C=C bond, such as norbornene or morpholinocyclohexene, resulted in the fused-skeleton dihydrothiazines **225** and **226**. The stereochemistry of the products was not investigated [75AG816; 77CB2114; 84ZN(B)1442].



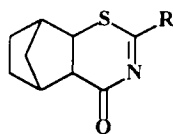
$\alpha$ -Lithiated isocyanides reacted with episulfides to give 3-mercaptoalkyl isocyanides, which were cyclized to the fused-skeleton dihydrothiazines **227**–**229** in 68–82% yields in the presence of copper(I) oxide. The cyclization yields the *trans*-fused isomers selectively, but **228** and **229** are epimers at C-4 (79LA451).



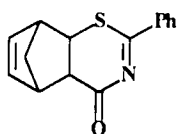
### 3. Dihydro-1,3-thiazin-4-ones

Similarly to the dihydrooxazinones (Section II,A,5), the title compounds can be prepared by the cycloaddition of thioacyl isocyanates to cycloalkenes containing an activated C=C bond.

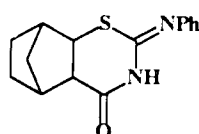
The addition of thiobenzoyl isocyanate to norbornene and norbornadiene resulted in the thiazinones **230** (R = Ph) and **231**, respectively (67CB685). The *tert*-butyl- and mesityl-substituted analogs of **230** were prepared by the same method. In the case of a benzyl substituent, the derivative **232** containing an *exo* double bond was formed (81CB549).



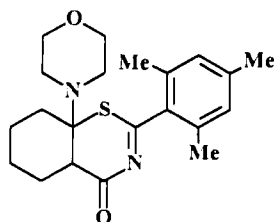
230



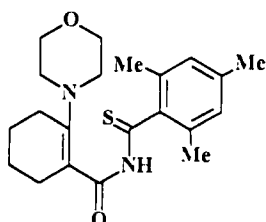
231



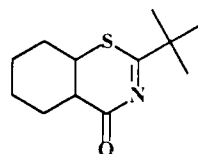
232



233



234



235

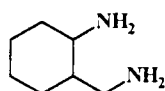
The similar addition of a mesityl-substituted isocyanate to 1-morpholinocyclohexene gave the dihydrothiazinone **233**, which is in ring-chain equilibrium with **234**. In the attempted preparation of the *tert*-butyl-substituted derivative, the tetrahydrobenzothiazinone **235** was formed by loss of morpholine (81CB549).

The cycloadditions of thioacyl isocyanates proceeded with *exo* and *cis* selectivity.

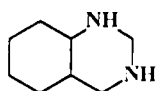
### C. SYNTHESIS OF PYRIMIDINES

#### 1. Tetrahydropyrimidines

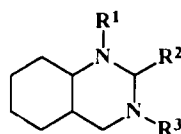
The parent perhydroquinazoline diastereomers were synthesized by Armarego in the late 1960s. Reduction of 5,6,7,8-tetrahydroquinazoline with sodium in ethanol resulted in the *trans*-fused perhydroquinazoline **237** exclusively [69JCS(C)1635]. Both *cis* and *trans* isomers were prepared in an alternative way: reaction of the *cis* and *trans* diamines **236** with formalde-



236



237



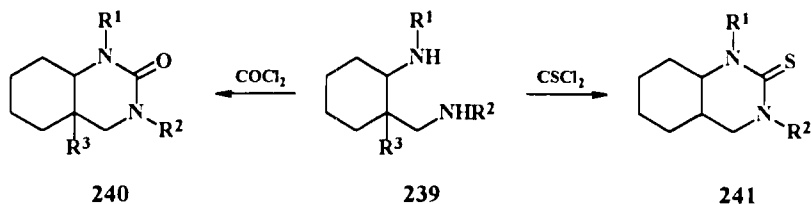
238

hyde gave the *cis* and *trans* **237**, respectively. Later, all four enantiomers of **237** were prepared in the same way [70JCS(C)1597]. For stereochemical investigations, a number of N-1, N-3, and C-2 methyl-substituted derivatives of **238** (*cis* or *trans*;  $R^1$ ,  $R^2$ ,  $R^3$  = H, Me) were also prepared, from the correspondingly substituted diamine and formaldehyde or acetaldehyde [71JCS(C)2502; 74JCS(P1)2313; 88T1465].

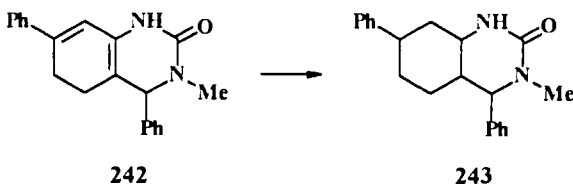
## 2. 2-Oxo, 2-Thioxo, and 2-Imino Derivatives

The methods used for the preparation of these compounds can be divided into four groups: (i) insertion of C-2 into a diamine, (ii) reduction of unsaturated derivatives, (iii) addition to the annelated C=C bond of quinazolines, and (iv) cycloaddition.

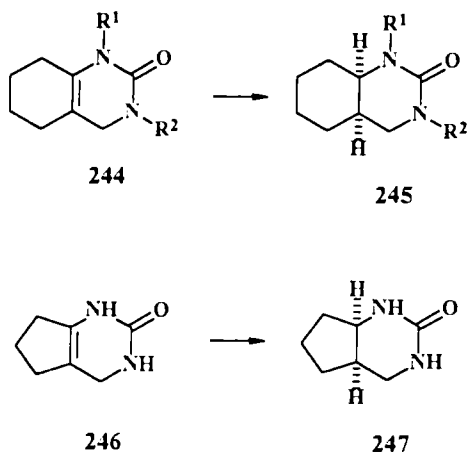
Through the cyclization of *cis* and *trans* 1,3-diamines **239** with phosgene, thiophosgene, or carbon disulfide, perhydroquinazolin-2-ones **240** and -2-thiones **241** (*cis* or *trans*;  $R^1$ ,  $R^2$ ,  $R^3$  = H, Me) can readily be prepared [71JCS(C)238, 71JCS(C)1812; 74JCS(P1)2313; 75JCS(P1)1471]. Attempts to thiate ureas **240** with phosphorus pentasulfide to give thioureas **241** were unsuccessful [75JCS(P1)1471].



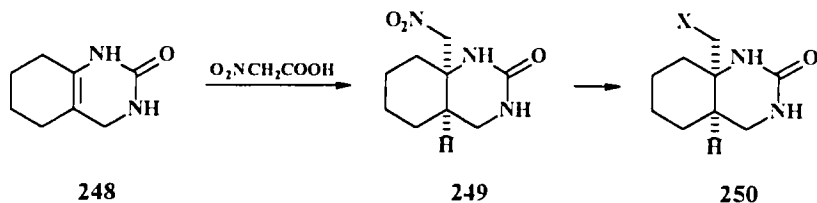
The reduction of quinazolinone **242** with hydrogen at 3 atm in the presence of a palladium-on-calcium-carbonate catalyst furnished perhydroquinazolinone **243**. The stereochemistry of **243**, with four chiral centers, was not investigated (70M1767).



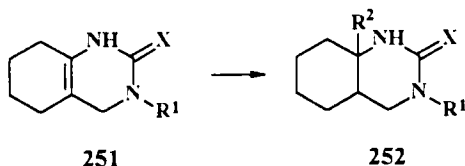
Armarego studied the reduction of quinazolinones **244** and cyclopentapyrimidinones **246**. The reduction with platinum(IV) oxide as catalyst was found to be highly stereospecific, resulting only in the *cis*-fused derivatives **245** and **247**, respectively [74JCS(P1)2313; 76JCS(P1)1415].



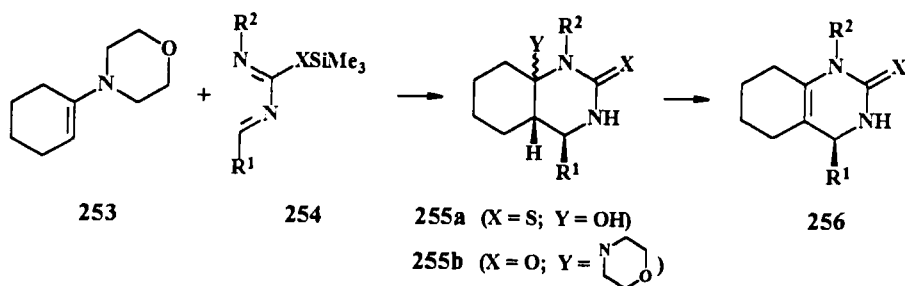
The reaction of 3,4,5,6,7,8-hexahydroquinazolin-2(1*H*)-one **248** and nitroacetic acid gave the 8a-nitromethyl-*cis*-octahydroquinazolinone **249** regiospecifically in high yield [71JCS(C)1812]. This reaction can proceed via a concerted mechanism, which explains the observed stereospecific addition [71JCS(C)3222]. A number of transformations of the nitro group were performed to obtain **250** ( $X = \text{NH}_2$ , Br, H, CN,  $\text{CONH}_2$ ,  $\text{COOH}$ ,  $\text{COOMe}$ ,  $\text{OAc}$ , OH) [71JCS(C)1812; 75JCS(P1)1471].



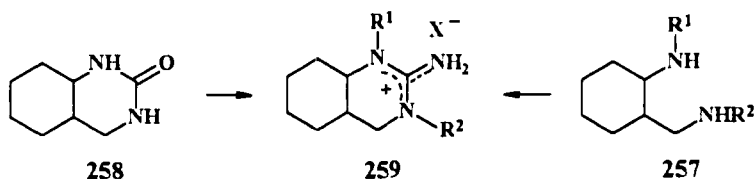
When the quinazolinones or thiones **251** ( $X = \text{O}$ , S;  $R^1 = \text{H}$ , Me,  $\text{CH}_2\text{Ph}$ ) were reacted with 2,4- or 2,6-dimethylphenol, an addition took place, resulting in the 8a-(2-hydroxy-3,5-dimethylphenyl)- or the 8a-(4-hydroxy-3,5-dimethylphenyl)-substituted quinazolinone **252** (70M1745). The stereochemistry of **252** was not investigated.



The reactions of 2-trimethylsilyloxy- (**254**, X = O) or 2-trimethylsilylthio-1,3-diazabutadienes (**254**, X = S) ( $R^1$ ,  $R^2$  = aryl, heteroaryl) and morpholinocyclohexene **253** yielded quinazolinones **255** regio- and stereoselectively by [4+2] cycloaddition. The relative configuration of the C-8a center was not determined because of the signal overlapping in the  $^1\text{H}$  NMR spectra. After aqueous workup, the cycloaddition resulted in the hydrolyzed and unhydrolyzed products **255a** and **255b**, respectively [94H(37)1109]. **255a** can be dehydrated to **256** directly, whereas **255b** requires preliminary hydrolysis [94H(37)1109].



The 2-aminoquinazolines **259** were prepared in two independent ways. The 2-quinazolinone **258** was transformed to 2-aminoquinazoline **259** by treatment with phosphorus oxychloride and subsequently with sodium amide in liquid ammonia, or with phosphorus pentachloride under carefully controlled conditions [75JCS(P1)1471]. Attempts to prepare the *N*-substituted derivatives failed, but the reaction was successful with the unsubstituted *cis* cyclopentane-fused homolog [76JCS(P1)1415].

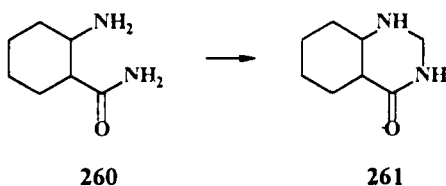


The reactions of the diamines **257** (*cis* or *trans*;  $R^1$ ,  $R^2$  = H, Me) and *S*-methylisothiuronium sulfates furnished the sulfates of aminoquinazolines **259** in good yields [70JCS(C)1597; 75JCS(P1)1471]. The four possible *N*-unsubstituted enantiomers of sulfates **259** were also prepared by this method [70JCS(C)1597]. The possible tautomerism of 2-aminoquinazolines **259** was not studied.

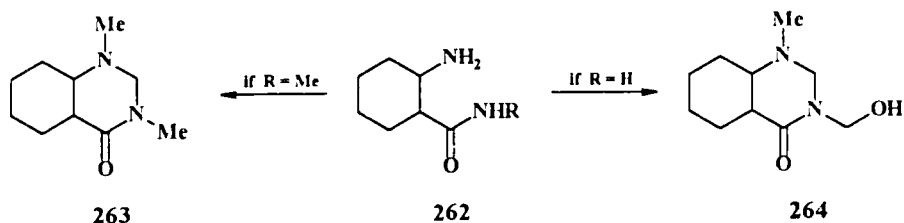
### 3. 4-Oxo Derivatives

A great number of 4-oxopyrimidines have been prepared by cyclization of  $\beta$ -amino acid derivatives with oxo reagents. All the compounds discussed here involve cyclohexane ring fusion, and therefore the quinazolinone nomenclature can be used.

The parent *cis*- and *trans*-octahydroquinazolin-4(1*H*)-ones **261** were synthesized by Armarego [71JCS(C)238] by the reaction of the *cis*- and *trans*-2-amino-1-carboxamides **260** with aqueous formaldehyde. The yields were only moderate.

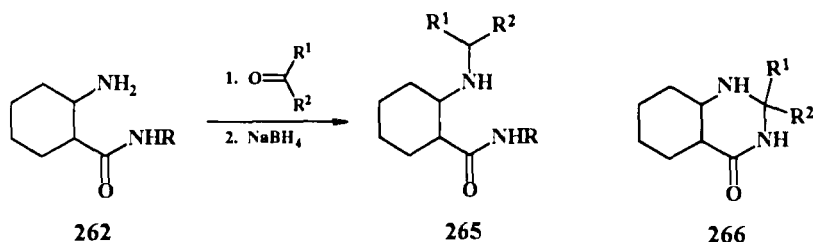


When a formaldehyde/formic acid mixture was used for cyclization of the *cis* and *trans* isomers of **262** (R = H, Me), interesting transformations were observed. In the reactions of methylcarboxamides **262** (R = Me), ring closure and *N*-methylation took place, resulting in 1,3-dimethyloctahydroquinazolinones **263**. Under the same conditions, in the reactions of the unsubstituted amides, ring closure, reductive methylation and hydroxymethylation on the amide nitrogen took place, resulting in the 1-methyl-3-hydroxymethyloctahydroquinazolin-4-ones **264** (87TL115).

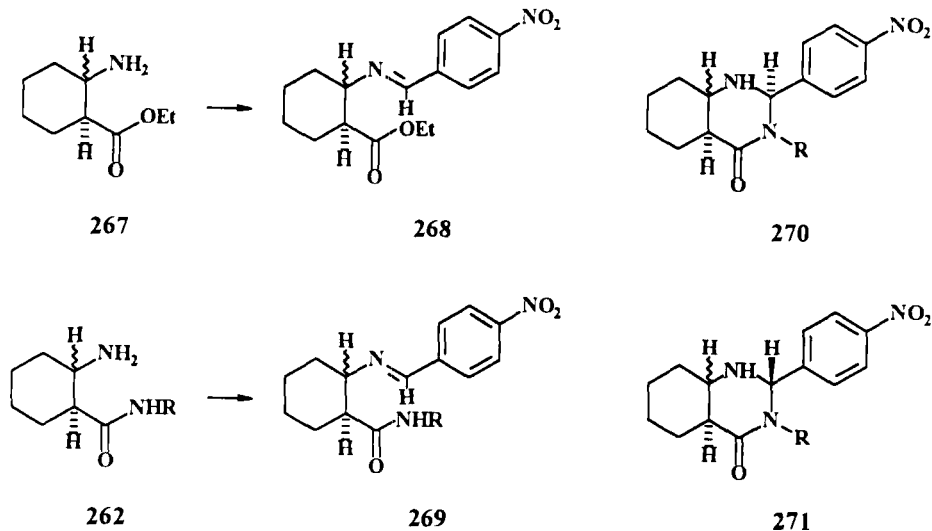


Reductive alkylation of carboxamides **262** with sodium borohydride in the presence of an oxo compound furnished the carboxamides **265**. In this process for the *cis* or *trans* isomers of **262** with acetone or cyclohexanone, the quinazolinone intermediates **266** [R<sup>1</sup> = R<sup>2</sup> = Me; R<sup>1</sup>, R<sup>2</sup> = (CH<sub>2</sub>)<sub>5</sub>] of the reductive alkylation were also isolated and characterized [87-ACSA(B)228; 91AX(C)2632].





Three of the four possible diastereomers of 2-aryloctahydroquinazolinones **270** and **271** were prepared from the amino esters **267** or carboxamides **262** (87T4731). In the reactions of the *cis* and *trans* esters **267** with 4-nitrobenzaldehyde, the *E*-benzylidene derivative **268** was formed in nearly quantitative yield. The ring closure with ammonia or methylamine gave two *cis*- and one *trans*-fused quinazolinones **270** and **271**. In the reactions of the carboxamides **262** and 4-nitrobenzaldehyde, quinazolinones **270** and **271** were again formed, in different ratios. The product distributions are given in Table III. The C-2 epimeric quinazolinones were separated by fractional crystallization, and the relative configurations were determined by X-ray diffraction (87T4731).

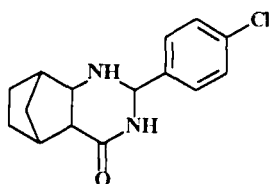


The *diendo*- and *diexo*-norbornane- and norbornene-fused quinazolinones **272** and **273** were prepared from the corresponding carboxamides and 4-chlorobenzaldehyde (87CB259).

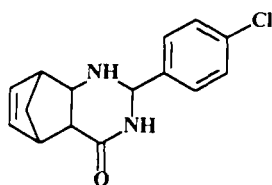
TABLE III  
PRODUCT DISTRIBUTIONS IN CYCLIZATIONS TO 2-ARYLOCTAHYDRO-4(1*H*)-QUINAZOLINES

Starting compound	Reaction conditions	<b>270a</b> ( <i>r</i> -4a, <i>c</i> -2, <i>c</i> -8a)	<b>270b</b> ( <i>r</i> -4a, <i>c</i> -2, <i>t</i> -8a)	<b>271a</b> ( <i>r</i> -4a, <i>t</i> -2, <i>c</i> -8a)	<b>271b</b> ( <i>r</i> -4a, <i>t</i> -2, <i>t</i> -8a)	<b>269</b> ( <i>cis</i> )	<b>269</b> ( <i>trans</i> )
<b>267</b> ( <i>cis</i> )	NH <sub>3</sub> or MeNH <sub>2</sub>	5	—	2	—	3	—
<b>267</b> ( <i>trans</i> )	NH <sub>3</sub> or MeNH <sub>2</sub>	—	—	—	9	—	1
<b>262</b> ( <i>cis</i> )	HOCC <sub>6</sub> H <sub>4</sub> NO <sub>2</sub> ( <i>p</i> ) RT	—	—	2	—	8	—
<b>262</b> ( <i>cis</i> )	HOCC <sub>6</sub> H <sub>4</sub> NO <sub>2</sub> ( <i>p</i> ) Δ	2	—	3	—	5	—
<b>262</b> ( <i>trans</i> )	HOCC <sub>6</sub> H <sub>4</sub> NO <sub>2</sub> ( <i>p</i> ) RT	—	—	—	7	—	3
<b>262</b> ( <i>trans</i> )	HOCC <sub>6</sub> H <sub>4</sub> NO <sub>2</sub> ( <i>p</i> ) Δ	—	—	—	8	—	2

<sup>a</sup> Data from Fülöp *et al.* (87T4731).

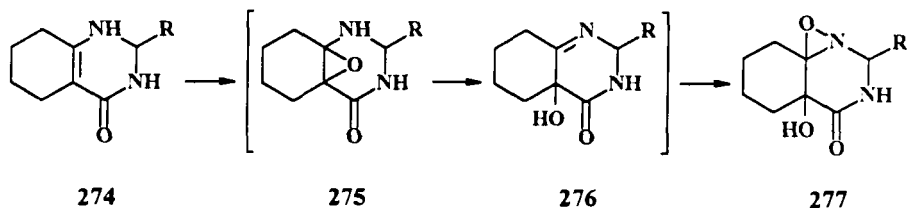


**272**



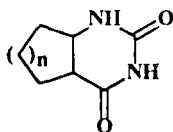
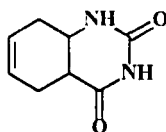
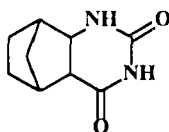
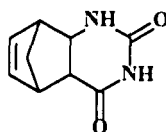
**273**

The synthesis of oxaziridine-fused quinazolinones **277** follows a different route. Quinazolinones **274** (R = Et, *n*Pr, *n*-hexyl) can readily be prepared by reacting 2-oxo-1-cyclohexanecarboxamide with aldehydes in the presence of ammonia solution. In the reaction of **274** and monoperoxyphthalic acid, the hydroxyoxaziridines **277** were formed via the presumed intermediates **275** and **276**. No spectroscopic evidence was given for **277**, nor was its relative configuration investigated [76JPR(318)895].

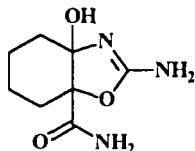
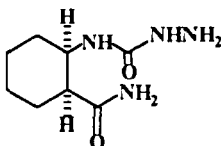
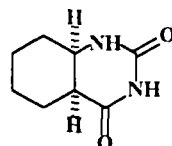


## 4. 2,4-Dioxo and 4-Oxo-2-thioxo Derivatives

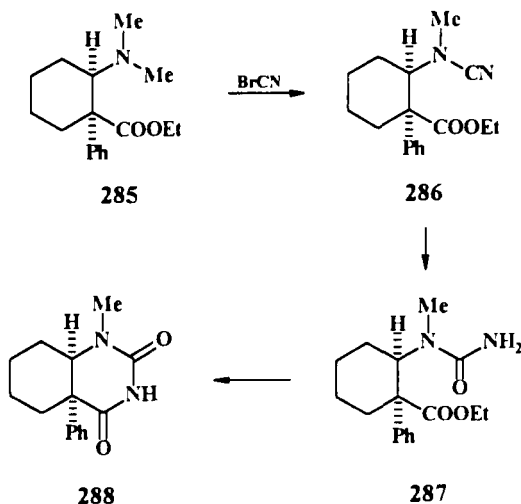
The unsubstituted parent compounds **278** (*cis*,  $n = 1, 2$ ; *trans*,  $n = 2$ ) and further analogous derivatives **279–281** were prepared by the same method in the reactions of the appropriate ethyl 2-amino-1-carboxylate hydrochloride and potassium cyanate, yielding the urea esters, which were cyclized without purification in boiling xylene (68MI1, 68MI2; 69T3807; 92JHC221). In the cyclization of ethyl *trans*-2-amino-1-cyclohexanecarboxylate hydrochloride, *trans*  $\rightarrow$  *cis* isomerization took place, resulting in a *cis-trans* mixture of **278** (92JHC221).

**278****279****280****281**

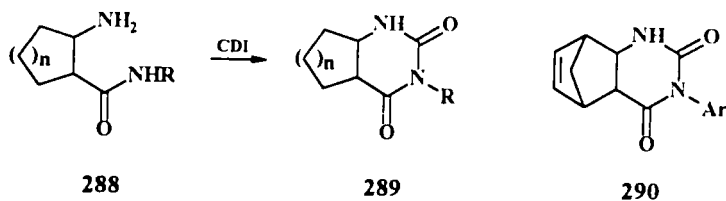
In the reaction of 1-hydroxy-2-oxo-1-cyclohexanecarboxamide and cyanamide, the 2-aminooxazole **282** was formed. Treatment of **282** with hydrazine yielded the semicarbazide **283**, which on iodine oxidation gave the perhydro-2,4-quinazolinedione **284** (87JPR177). Although the configuration of the product was not given, the *cis* annelation can be deduced from the published  $^{13}\text{C}$  NMR data.

**282****283****284**

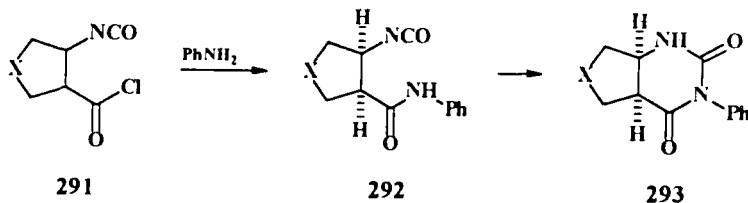
The cyclization of **285** proceeded similarly as in the synthesis of **278–281**. The *N,N*-dimethyl-substituted amino ester **285** and cyanogen bromide resulted in **286**, and subsequent acid hydrolysis led to the urea ester **287**, which was cyclized to 1-methylperhydro-2,4-quinazolinedione **288** at elevated temperature [69LA(728)64].



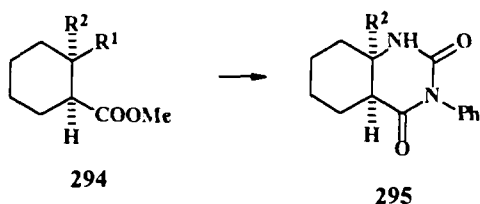
2-Amino-1-carboxamides **288** (*cis*,  $n = 1, 2$ ; *trans*,  $n = 2$ ;  $R = \text{Ph}$ , substituted aryl) were cyclized to dihydrouracils **289** with 1,1'-carbonyldiimidazole (CDI) with the retention of configuration (90T1943). The *diexo*-fused **290** was prepared by the same method (87T1921).



The isocyanato acid chloride **291** ( $X = \text{CH}_2\text{CH}_2$ ,  $\text{CH}=\text{CH}$ ), prepared through trimethylsilyl esters (Section II,A,4), reacts with aniline to give the isocyanato carboxamide **292**, which readily yields the quinazolinodione **293** (73AG86; 75LA1387). Armarego has prepared the quinazolinodiones

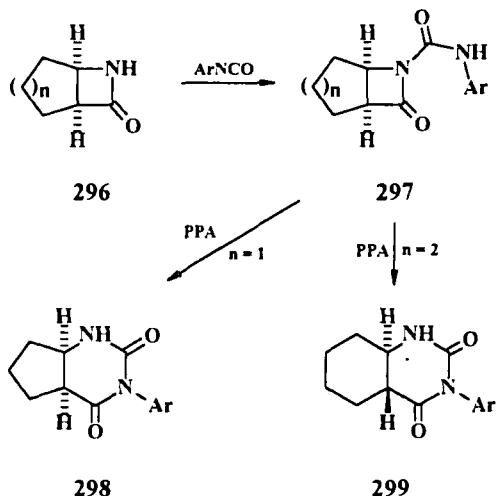


**295** from ureido esters **294** ( $R^1 = \text{NHCOPh}$ ;  $R^2 = \text{Me}$ ,  $\text{CH}_2\text{NH}_3\text{Cl}^+$ ,  $\text{CH}_2\text{Br}$ ) by methanolic sodium hydroxide treatment. The ureido esters **294** were obtained in two ways: by treatment of the corresponding amino ester with



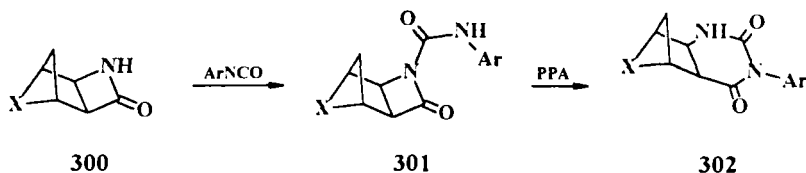
phenyl isocyanate, or from the isocyanato carboxylate **294** ( $R^1 = \text{NCO}$ ) with aniline.

The 3-aryl-substituted pyrimidinediones **298** and **299** were formed in ring enlargements of **297**. The urea derivatives **297** ( $n = 1, 2$ ) were prepared by reaction of the *cis* azetidinones **296** ( $n = 1, 2$ ) and aryl isocyanates. On heating in PPA, the cyclopentane- and cyclohexane-fused *cis* azetidinones **297** underwent transamidation with ring enlargement to yield the *cis*- and *trans*-fused pyrimidinediones **298** and **299**, respectively (90T1943). In the transamidation, the attack of the more nucleophilic nitrogen on the carbonyl group of the strained four-membered ring gives the cyclopentane *cis*-fused derivatives **298** with retention, whereas the analogous reaction of the *cis* cyclohexane derivatives **297** ( $n = 2$ ) takes place with inversion and results in the thermodynamically favored *trans* isomer **299**.

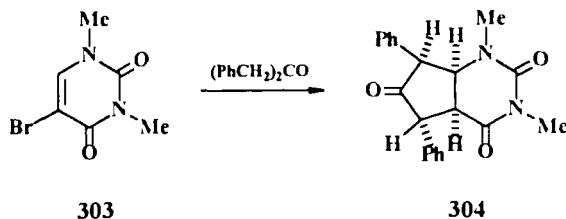


A similar observation was made in the transformations of the norbornane and norbornene *diexo*-fused azetidinones **300** ( $X = \text{CH}_2\text{CH}_2$ ,  $\text{CH}=\text{CH}$ ) to *diexo*-methanoquinazolinediones **302** (87T1921).

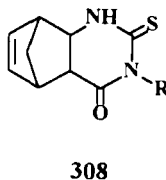
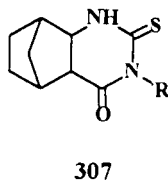
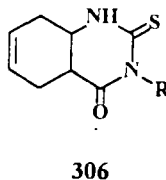
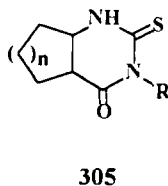
The C—C bond formation of 5-bromouracil derivatives with carbanions gave a new possibility for the preparation of cyclopentanone-fused pyrimi-



dinediones. The reaction of 5-bromo-1,3-dimethyluracil **303** with a carbanion generated from dibenzylketone with sodium ethoxide gave the *cis*-fused pyrimidinedione **304** stereospecifically [89JCS(CC)1659].



The parent 4-oxo-2-thioxopyrimidines **305** (*cis*,  $n = 1, 2$ ; *trans*,  $n = 2$ ;  $\text{R} = \text{H}$ ), **306** (*cis* or *trans*), **307** and **308** (*diendo* and *diexo*) were prepared analogously to pyrimidinediones: by reacting the corresponding amino ester hydrochlorides with potassium thiocyanate (89MRC959), or from alicyclic ethyl 2-isothiocyanato-1-carboxylates, obtained by the reaction of amino esters and thiophosgene with ammonia (96UP2).



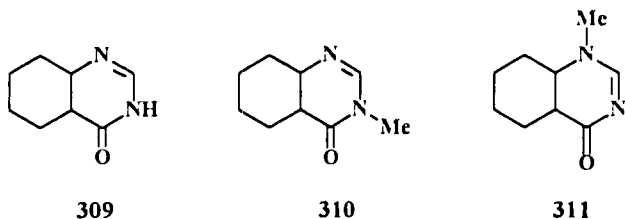
A number of substituted derivatives of **305** (*cis*,  $n = 1, 2$ ; *trans*,  $n = 2$ ), **306** (*cis* or *trans*), **307**, and **308** (*diendo* and *diexo*) ( $\text{R} = \text{Me}$ ,  $\text{Et}$ ,  $\text{Ph}$ , substituted aryl) were prepared from the corresponding amino acids with isothiocyanate and acidic ring closure of the resulting thiocarbamide

adduct [85ACH(118)71, 85JCS(P1)2483]. The *N*-methyl-substituted derivatives of the *diendo* and *diexo* isomers of **308** were likewise prepared from the foregoing ethyl 2-isothiocyanato-1-carboxylates with methylamine (96UP2). In the reactions of cyclic ketones with isothiocyanates, 2,4-thioxoperhydroquinazoline and its 5,8-methano derivative were prepared [70CR(C)1592].

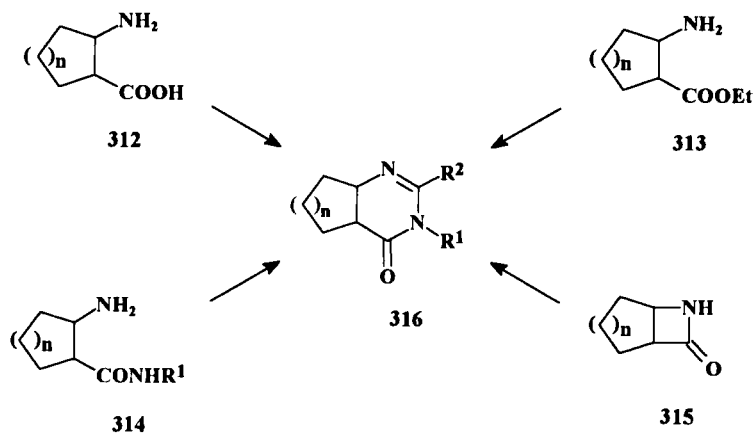
### 5. Dihydropyrimidines and Dihydropyrimidin-4-ones

A few 1,4,5,6- and 3,4,5,6-tetrahydropyridine derivatives have been prepared and patented, but their stereostructures were not determined. In these syntheses, 2-aminomethyl-1-cyclopentylamine or -1-cyclohexylamine or their substituted derivatives were used in the cyclocondensations with carboxylic acid esters or with aldehydes in the presence of sulfur [72-GEP2040502, 72GEP2107348; 73GEP2132079; 78GEP2701372; 80GEP-2830590, 80GEP2835029; 81GEP3004903; 82IJC(B)4].

The parent compound **309** was synthesized by the reactions of *cis*- or *trans*-2-amino-1-cyclohexanecarboxamides with ethyl orthoformate [69-JCS(C)1635; 71JCS(C)238]. In principle, **309** can exist in five tautomeric forms: two enol forms, one lactim form, and the 1*H* and 3*H* forms, of which the two enol forms can be excluded because no *cis-trans* isomerization was observed. The 1*H* and 3*H* forms may be fixed with substituents; hence, **310** and **311** with fixed tautomeric structures were prepared. The UV spectra reveal that the unsubstituted derivatives exist in 3*H* form, as shown for structure **309** [71JCS(C)238].



Because some of the compounds with general structure **316** have noteworthy pharmacological activities, a number of alternative methods have been developed for the synthesis of the 2-substituted and 2,3-disubstituted derivatives **316**. 2-Substituted derivatives of **316** (*cis*, *n* = 1, 2, 3, 4; *trans*, *n* = 2, 3, 4) were prepared (77GEP2643384; 80AUP507798) from **312–315** with ethyl benzimidates. The attempted ring closure of *trans*-2-amino-1-cyclopentanecarboxylic acid to *trans*-fused derivatives failed. In this reac-

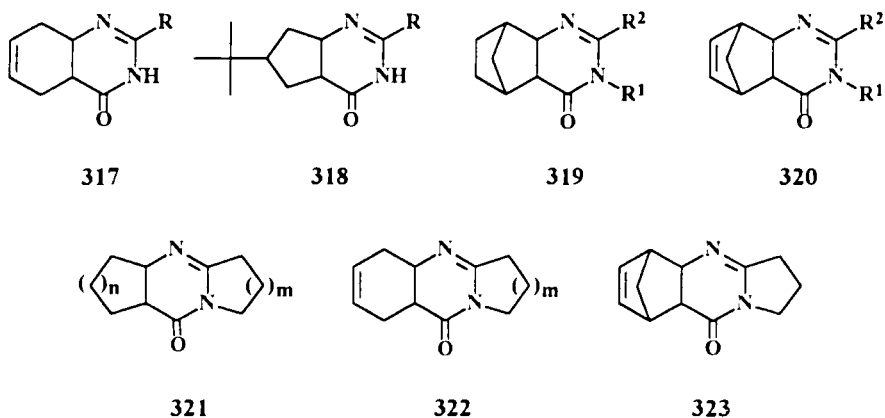


tion, slow isomerization of the *trans* amino acid and subsequent cyclization to *cis*-fused pyrimidinone **316** ( $n = 1$ ) took place.

From *N*-substituted carboxamides, the 3-unsubstituted derivatives were formed, with loss of the corresponding amine. This reaction is to be expected from the mechanism of the ring closure: amidine formation and subsequent nucleophilic attack of the amidine nitrogen on the carbonyl group.

For the *cis* azetidinones **315**, the first step is the formation of an amidine intermediate, followed by ring enlargement with transamidation [96-H(42)625]. The preceding amidine structure was revealed by TLC on silica gel when the formation of derivatives **316** was investigated (89MI1).

The 2,3-disubstituted derivatives **316** are easily obtained by the cyclization of carboxamides **314** with orthoesters.





The foregoing methods have also been used to prepare further related derivatives **317–320** [85T1353; 87CB259, 87JCS(P1)237, 87S290; 96H(42)625].

The attempted 4-oxo  $\rightarrow$  4-thioxo exchange with  $\text{P}_4\text{S}_{10}$  resulted in an aromatized structure instead of the expected 4-thioxo derivative [85-ACH(118)49].

The tri- and tetracyclic derivatives **321–323** were prepared in the reactions of **312–315** and lactim ethers instead of acyclic imidates [79JCS(P1)1765; 82JCS(P1)2801; 83JCS(P2)237; 90PHA109; 94MI1].

#### D. CORRELATION OF REACTIVITY, RING SIZE, AND RING FUSION

In the ring closures of the 1,2-disubstituted 1,3-difunctional cyclohexane, cycloheptane, and cyclooctane derivatives discussed in Sections II,A,B, and C, no appreciable differences were found in the reactivities of the *cis* and *trans* isomers. In contrast, very significant differences were observed in the cyclization reactivities of the *cis* and *trans* 1,2-disubstituted 1,3-difunctional cyclopentane derivatives, such as 1,3-amino alcohols, 2-hydroxy-1-carboxamides or  $\beta$ -amino acids. Whereas the *cis* isomers reacted readily, their *trans* counterparts did not undergo ring closure in most cases. This difference was manifested in the formation of both “*d*”- and “*e*”-fused derivatives.

For example, *trans*-2-hydroxy-1-cyclopentanecarboxamide could not be cyclized with aldehydes or ketones to the corresponding cyclopentane-fused 1,3-oxazin-4-ones. This permitted a facile isomer separation (Section II,A,3).

*trans*-2-Hydroxymethyl-1-cyclopentylamine and *trans*-2-aminomethyl-1-cyclopentanol could not be transformed to 1,3-oxazines with aldehydes (Section II,A,1).

*trans*-2-Amino-1-cyclopentanecarboxylic acid or carboxamide could not be cyclized to the corresponding *trans*-fused dihydropyrimidinone; instead, a slow racemization took place and the *cis*-fused pyrimidinone was formed (Section II,C,2).

Finch *et al.* described the separation of *cis*- and *trans*-2-hydroxymethyl-1-cyclopentanol, based on the fact that the *trans* compound did not undergo ring closure to 1,3-dioxane (75JOC206).

In agreement with these observations, kinetic studies on  $\text{N} \rightarrow \text{O}$  acyl migrations and ring-chain tautomerism have quantitatively confirmed the differences just mentioned.

The  $N \rightarrow O$  acyl migration of the *N*-acyl derivatives of *cis*- and *trans*-2-aminomethyl-1-cyclohexanol, *cis*- and *trans*-2-hydroxymethyl-1-cyclohexylamine, and the homologous cyclopentane, cycloheptane, and cyclooctane derivatives, which occurs through a tetrahydro-1,3-oxazine-type transition state, has been studied in detail. Though the *trans* 1,3-amino alcohols of six-, seven-, and eight-membered alicyclic rings display somewhat higher reaction rates than their *cis* counterparts, the rates of the acyl migration reactions do not differ by an order of magnitude ( $k_{trans}/k_{cis} = 2-4$ ) [68TL2713; 70ACH(65)347; 71MI1; 72MI2; 73MI; 75ACH(81)187; 77MI2]. In contrast, the acyl migrations of the *cis* and *trans* cyclopentane derivatives exhibited striking differences of several orders of magnitude in favor of the *cis* isomer [68TL4441; 72ACH favor of the *cis* isomer [68TL4441; 72ACH(74)479].

The ring-chain tautomerism of tetrahydro-1,3-oxazines is very sensitive to the stability differences, the substituents and the ring-fusion effect (Section IV,A). It also reveals a considerable stability difference in favor of the *cis* isomers. In the reactions of the *cis*- and *trans*-2-amino-1-cyclohexanols, as compared with the hydrindane analog systems, where the heteroatoms form an oxazolidine ring *cis*- or *trans*-fused with cyclohexane, the corresponding stability differences were again found to be in favor of the *cis* isomer (93JOC1967).

It is worthwhile to compare the stability differences of the analogous hydrindanes and decalins. In both cases, the Gibbs standard free energy differences favor the *trans* isomers, by 1.3 kJ mol<sup>-1</sup> in the hydrindanes and by about 10 kJ mol<sup>-1</sup> in the decalins (94MI3). This direction of the difference is in contrast with that found for the 1,3-heteroanalogs of *cis*- and *trans*-hydrindane.

Independently of the foregoing differences, the ring closures of *trans*-1,2-disubstituted 1,2- and 1,3-difunctional cyclopentane derivatives to cyclopentane *trans*-fused six-membered 1,3-heterocycles were successfully performed in some cases. For example, with cyclopentane *trans*-fused 1,3-oxazin-2-ones, 2-thiones (83T1829; 86CB575), 2-imino derivatives (85T5981), *N*-substituted tetrahydro-1,3-oxazines (87T1863), where the possibility of ring-chain tautomerism is excluded, and dihydrothiazines [85ACH(118)37; 86JST(140)327] were synthesized without difficulty.

The preceding differences and similarities indicate a considerable difference in the stabilities of *cis* and *trans* cyclopentane-fused heterocycles as compared with those of the higher homologs. Such differences are especially striking when the formation of the heterocycles proceeds through an equilibrium reaction.

### III. Stereochemistry and Conformational Analysis

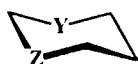
#### A. GENERAL CONSIDERATIONS

##### 1. Methods

The most useful methods for elucidation of the structure of the title compounds are  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectroscopy, which have been extensively applied for determination of their conformations and configurations. Geminal and vicinal H,H-coupling constants and  $^{13}\text{C}$  chemical shifts (together with dynamic NMR measurements) (80MI2; 86MRC145; 87MI1; 92MI2; 93MI2; 94MI3; 94MI2) have proved to be the most informative structural parameters, although crystal structures determined by X-ray diffraction (Section III,B,6) are sometimes also very helpful.

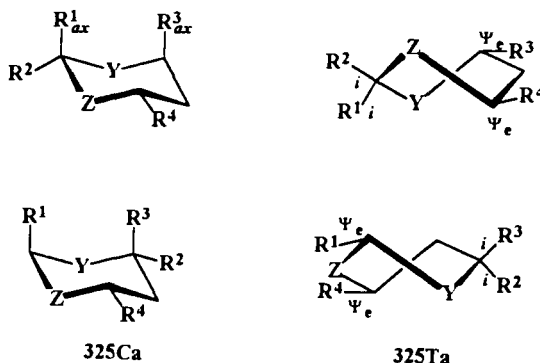
##### 2. Monocyclic Six-Membered (1,3-Hetero)cyclanes

a. *Cyclohexane Derivatives.* Cyclohexane greatly favors the chair conformation (94MI3) **324C**, although a special substitution (e.g., *trans*-di-*tert*-butyl substitution [74JCS(P2)890]) may force it into the twist form **324T** [ $\Delta G^\circ_{\text{CT}} = 20.5 \text{ kJ mol}^{-1}$ ;  $\Delta H^\circ_{\text{CT}} = 24.7 \text{ kJ mol}^{-1}$ ;  $\Delta S^\circ_{\text{CT}} = 14.6 \text{ J mol}^{-1} \text{ K}^{-1}$

**324C****324T****325C****325T<sub>1</sub>****325T<sub>2</sub>**

(74MI1)]. In 1,3-diheterocyclohexanes, the chair form **325Ca** likewise is the greatly predominating conformation, although the two twist forms, the 1,4- (or 3,6-) **325T<sub>1</sub>** and 2,5-twists **325T<sub>2</sub>**, become accessible, especially when the chair form contains two *syn*-axial methyl or other substituents (as in **325Ca**), which in the twist forms **325Ta** assume isoclininal (i) and/or pseudo-equatorial ( $\psi_c$ ) orientations (82JOC4688; 94JOC2138; 94MI2). Table IV lists the conformational energies of methyl groups in several 1,3-diheterocyclohexanes.

The conformational analysis of methyl-substituted tetrahydro-1,3-oxazines has been discussed in detail in several contexts (86MRC145,



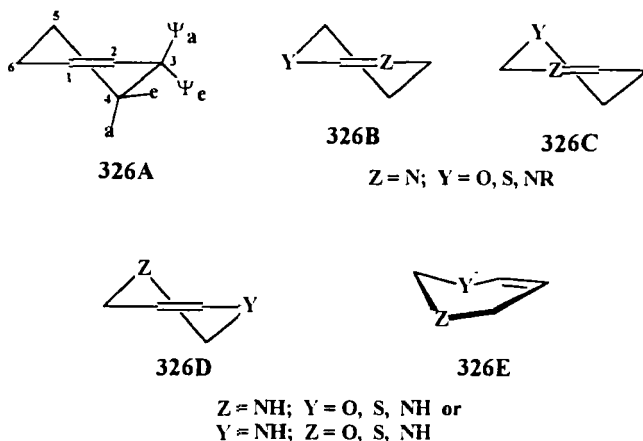
86MRC480; 87MI1; 94MI3). In tetrahydro-1,3-oxazines (and hexahydropyrimidines), the C-2 epimeric equilibria are established instantaneously via the open-chain tautomers, although both isomers can be seen by NMR (87MI1; 94MI2; 94MI3). The same situation has been reported for the *N*-substituted derivatives (84T3587), although their equilibration is slow and occurs via a protonated Schiff base intermediate (84T3587; 94MI3). Conformational isomerization of hexahydropyrimidines has been described [67JCS(B)560; 68T829].

b. *Cyclohexene Derivatives.* Cyclohexene attains a half-chair conformation (89MI2; 94MI3) where C-3 and C-6 lie in the plane of the double bond (**326A**). This means that the methylene hydrogens or the respective substituents at these positions ( $\omega_{3,6}$  ca.  $15^\circ$ ) are not truly axial or equatorial; such groups are called pseudoaxial ( $\psi_a$ ) or pseudoequatorial ( $\psi_e$ ) and the situation is also reflected in the magnitude of the conformational energies (94MI3). The hydrogen atoms/substituents at positions 4 and 5 ( $\omega_{4,5}$  ca.  $60^\circ$ ) are in turn truly axial and equatorial (94MI3). The inversion barrier in cyclohexene is about 22 kJ mol<sup>-1</sup> (94MI3). 1,3-Diheterocyclohexenes

TABLE IV  
CONFORMATIONAL ENERGIES (94MI2) IN kJ mol<sup>-1</sup> OF THE AXIAL METHYL GROUPS IN  
DIHETEROCYCLOHEXANES (cf. CYCLOHEXANE 7.5 kJ mol<sup>-1</sup>)

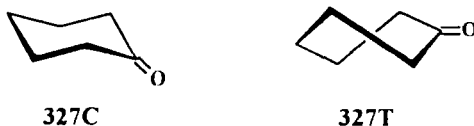
Methyl position	Compound						Y
	O,O	O,N	O,S	N,S <sup>a</sup>	N,N <sup>a</sup>	<i>d</i> <sub>C-N</sub> /pm	
2a	17.0	15.6	13.6	12.2	14.2	1.41	O
4a	12.2	10.9	7.5	10.9	10.9	1.47	N
5a	3.6	5.4	3.7	5.5	7.2	1.82	S
6a	12.3	12.2	12.3	8.9	10.9		

<sup>a</sup> Estimated; e.g.,  $\Delta G^\circ$  for 2a-Me in hexahydropyrimidine =  $2(15.6 - 17.0/2) = 2 \times 7.1 = 14.2$  kJ mol<sup>-1</sup>.



(70CB3242; 80MI2; 89MI2; 93MRC615) prefer half-chair conformations (**326B–326D**), which are sometimes very close to a sofa form (e.g., **326E**).

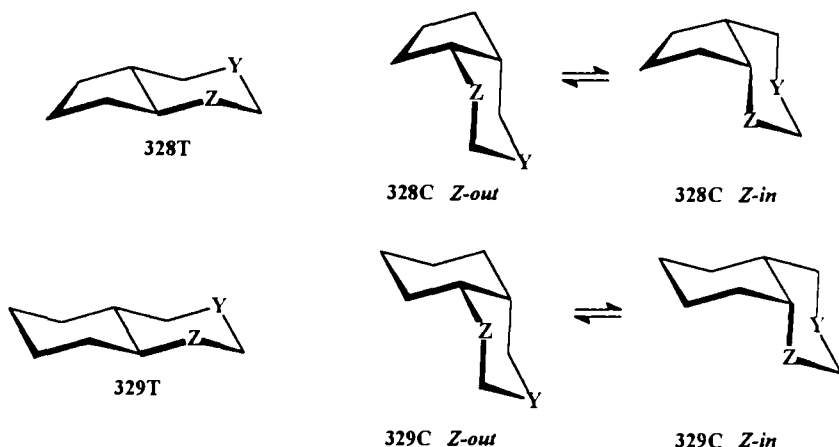
*c. Cyclohexanone Derivatives.* The most stable conformation of this molecule is a chair (**327C**), which is appreciably flattened at the carbonyl site [80JST(69)137; 94MI3], the  $H_{eq}-C-C=O$  torsion angle ranging from  $3.3^\circ$  to  $12.7^\circ$  (94MI3). This again has its consequences, especially as concerns the conformational energies of the substituents at position 2 (94MI3). The twist form **327T** has been calculated to be only  $11.4 \text{ kJ mol}^{-1}$  above the chair form (73JA4424).



### 3. Hydrindanes and Decalins

These molecules deserve special mention, since the cyclopentane- and cyclohexane-fused 1,3-diheterocyclohexanes dealt with are their hetero-analogs.

*a. Hydrindanes.* Entropy favors the *cis* isomer (**328C**) in the hydrindanes (94MI3) and the *trans* isomer (**328T**) is only slightly favored ( $\Delta G^\circ = 2.1 \text{ kJ mol}^{-1}$ ). The *trans* isomer **328T** exists in the practically anancomeric envelope–chair conformation, whereas the *cis* isomer **328C** can assume two interconverting envelope–chair conformations, the *Z-in* and *Z-out* forms. The enthalpy disadvantage of the *cis* isomer is partly relieved in the *Z-in* conformation of the cyclopentane-fused 1,3-diheterocyclohexanes, where



the methylene group ( $X = \text{CH}_2$ ) being pushed into the ring is replaced by a heteroatom ( $X = \text{O}, \text{S}, \text{NR}$ ;  $Y = \text{NR}$ ; or vice versa; see Table IV).

b. *Decalins*. The framework of *trans*-decalin is practically locked in the double chair conformation **329T**, since it cannot invert to the alternative chair–chair system and the chair–boat or boat–boat systems are of considerably higher energy (94MI3). The same situation prevails if the other ring is a fused 1,3-diheterocyclohexane ( $Z = \text{O}, \text{S}, \text{NR}$ ;  $Y = \text{NR}$ ; or vice versa). In contrast, *cis*-decalin and its hetero analogs have two interconverting chair–chair combinations (both chairs are interconverted), the *Z-in* and *Z-out* forms (**329C**).  $\Delta H^\circ_{\text{isom}} = 11.3 \text{ kJ mol}^{-1}$  in favor of *trans*-decalin.

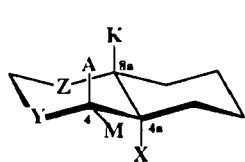
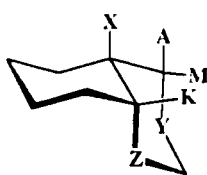
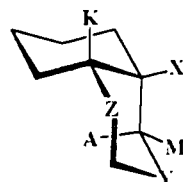
In the *trans*-decalin systems **329T**, the substituents occupy well-defined axial or equatorial positions, whereas in the mobile *cis*-decalin system **329C**, the substituents occupy either the equatorial or the axial orientation and, if the framework equilibrium is unbiased (as in decalin itself), the preferred conformation will be that with the equatorial substituent. Although this is mainly true for the 1,3-hetero analogs as well, there are also other factors (discussed later) to be taken into account.

## B. CONFORMATIONAL ANALYSIS OF CYCLOALKANE-FUSED 1,3-HETEROCYCLES

### 1. Tetrahydrooxazines, -Thiazines, and Hexahydropyrimidines

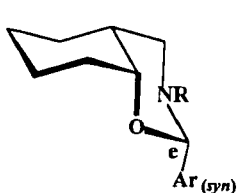
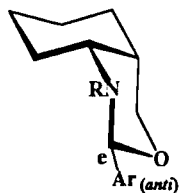
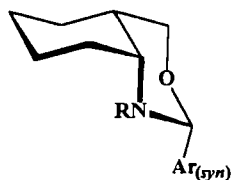
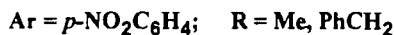
For these systems, the conformational studies have dealt practically only with 1,3-diheterocycles fused with cyclohexane. The *trans*-fused derivatives **330T** attain a biased chair–chair conformation which is easy to assign on

the basis of the AMKX-type spin system given by the protons on C-4 (H-4<sub>ax</sub> and H-4<sub>eq</sub>), C-8a [H-4a(ax)] and C-4a[H-8a(ax)], where the vicinal coupling constants  $J_{AX}$  ( $= J_{aa}$ ) and  $J_{KX}$  ( $= J_{aa}$ ) are 10–13 Hz and  $J_{MX}$  ( $= J_{ca}$ ) is 3–5 Hz [69JCS(C)1635; 72ACH(73)81; 80OMR204; 84T3587; 85ACH(118)187; 86MRC145; 94JOC5328]. Similarly, the  $^{13}\text{C}$  NMR spectra of the *trans* isomers **330T** are straightforwardly explainable with the biased double-chair conformation [80OMR204; 84T3587; 85ACH(118)187; 86MRC145; 94JOC5328; 96MRC998].

**330T****330C Z-in****330C Z-out**

The *cis*-fused derivatives **330C** can exist in two interconvertible chair-chair conformations (*Z-in* or *Z-out*), the contributions of which depend on the steric requirements of the groups attached to the annellation points, anomeric effects, and other nonbonded interactions [69JCS(C)1635; 72ACH(73)81; 74JCS(P1)2313; 80OMR204; 84T3587; 85ACH(118)187; 86MRC145; 88T1465; 89JCC265; 91JST(246)301; 92MI2; 93JCC944; 94JOC5328; 96MRC998].

In many cases, the *cis* isomers highly if not exclusively prefer either the *Z-in* or *Z-out* conformation (**330C**), as concluded from the values of the vicinal H,H-coupling constants and various shielding phenomena in both  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra; for example, the *cis*-fused *syn*-2-(*p*-nitrophenyl)octahydro-3-methyl (or benzyl) -2*H*-1,3-benzoxazines assume the *O-in* (**331**; all-*cis* configuration) and the corresponding *anti*-2-(*p*-nitrophenyl)octahydro-1-methyl (or benzyl), -2*H*-3,1-benzoxazines the *N-out* (**332**, *anti*-Ar configuration) conformations (80OMR204). The somewhat less stable ( $\Delta G^\circ = 1.7 \text{ kJ mol}^{-1}$ ) C-2 epimer of **332** (*N*-Me) in turn assumes

**331 O-in****332A N-out****332B N-in**

the *N-in* conformation (cf. *Z-in* of **330C**) to avoid the axial *p*-nitrophenyl group (84T3587).

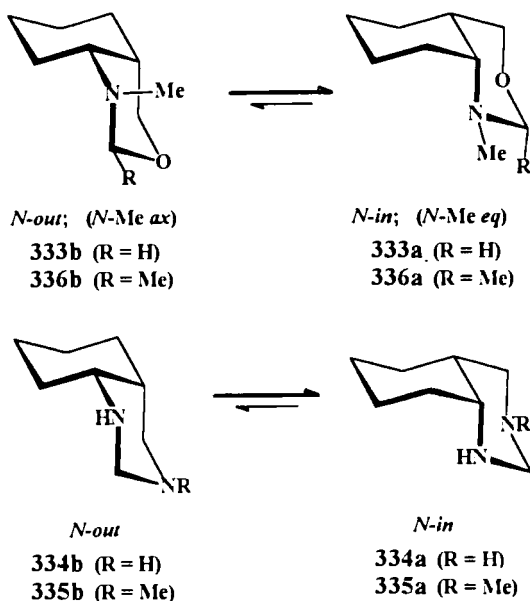
Indeed, the two main reasons for the change in conformation appear in general to be the highly preferred equatorial orientation of the C-2 substituent and the possibility that the *N*-methyl group assumes an axial orientation without *syn*-axial interactions [80OMR204; 84T3587; 96MRC998]. This is supported by the observation that the preferred epimer (*syn*-2-Ar) in both *cis*-fused 2-(*p*-nitrophenyl)octahydro-2*H*-1,3- and -3,1-benzoxazine appears to be the *Z-in* form of **330C** [73OMR159; 85ACH(118)187; 86MRC145]. If Z = O, the *syn*-axial interactions are minimized on going from the *O-out* to the *O-in* conformation, since the interactions due to the axial CH<sub>2</sub> groups are changed to those caused by the axial O and NR (Table I) and hence the latter conformation strongly predominates [80OMR204; 84OMR527; 96MRC998].

There are, however, several examples where the predominance of the *Z-in* or *Z-out* form of **330C** is not so evident [69JCS(C)1635; 74JCS(P1)2313; 84OMR527; 88T1465]. In a typical biased *Z-in* conformation, both  $J_{AX}$  (ca. 0–2 Hz) and  $J_{MX}$  (ca. 2–4 Hz) are relatively small, whereas in the *Z-out* conformation they are ca. 11–13 and 5 Hz, respectively [74JCS(P1)2313; 80OMR204; 86MRC145; 88T1465; 96MRC998]. In other words, one can assume that the predominance of the *Z-in* or *Z-out* form is almost exclusive if  $J_{AX} + J_{MX}$  is ca. 4–5 or 15–17 Hz, respectively. If the former is >6 Hz and the latter <15 Hz, it is most likely that a conformational equilibrium can be found between the two forms [74JCS(P1)2313; 88T1465; 96MRC998].

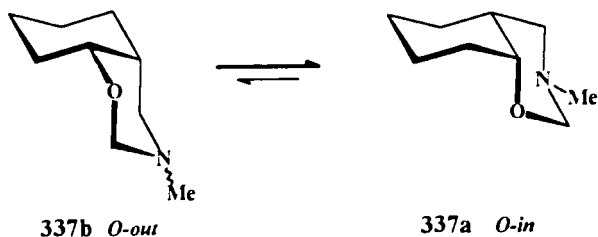
The most dramatic examples have been reported for *N*-methyl-*cis*-octahydro-2*H*-3,1-benzoxazine **333** [96MRC998], and for *cis*-decahydroquinazoline **334** and 3-methyl-*cis*-decahydroquinazoline **335** (88T1465).

For a discussion of the above cases, it is also important to mention that the geminal coupling constant,  $^2J_{2e2a}$ , depends practically only on the orientation of the lone pair on the nitrogen(s). This was first reported for tetrahydro-1,3-oxazines [68JCS(B)1224; 96MRC998] and later for decahydroquinazolines [71JCS(C)2502; 74JCS(P1)2313; 88T1465]. For **333a** (*N-in*), where *N*-methyl is equatorial, and for **333b** (*N-out*), where it is axial,  $^2J_{2e2a}$  [–7.5 and –10.8 Hz at 198 K, respectively, and on the average –8.5 Hz at 323 K in (CD<sub>3</sub>)<sub>2</sub>CO] is also an indicator of the conformational equilibrium [96MRC998]. The shielding effects on the <sup>1</sup>H and <sup>13</sup>C NMR chemical shifts and the values of the vicinal and geminal coupling constants at various temperatures [96MRC998] showed that **333** is a ca. 3:1 mixture of the *N-in* (**333a**) and *N-out* (**333b**) forms at 198 K, and a 7:3 mixture at ambient temperature (–Δ*G*<sup>o</sup> = 2.2 kJ mol<sup>–1</sup>). This is in good agreement with the C-2 epimer equilibrium [96MRC998] of 1,2-dimethyloctahydro-2*H*-3,1-benzoxazine ([**336a**]/[**336b**] = 3:2).





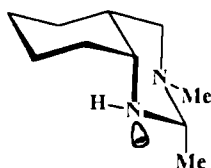
Incomplete spectral information and an ignorance of the steric requirements of the *N*-methyl substituent (or lone pair) led the authors of an earlier report (84OMR527) to conclude that **333** is conformationally homogeneous (**333b** instead of the predominance of **333a**; see earlier discussion). The latter result was later referred to in a review (92MI1) and in two molecular mechanics calculations [91JST(246)301; 93JCC944]. The calculations also failed to predict the conformational equilibrium of **333** or the strong predominance of **337a** (instead, **337b** was estimated to be favored by 4.7 and 3.2 kJ mol<sup>-1</sup>, respectively).



Booth *et al.* (88T1465) froze out the ring inversion in **334** and **335** to determine the conformational equilibria between the *N-in* and *N-out* forms and the orientation of the *N*-substituents. From integration of the frozen-in <sup>13</sup>C spectrum at 215 K ( $-\Delta G^\circ = 4.7$  kJ mol<sup>-1</sup>), and from the half-intensity width of the C-2 signal at 277 K ( $-\Delta G^\circ = 5.1$  kJ mol<sup>-1</sup>), the *N*-unsubstituted

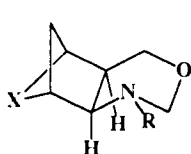
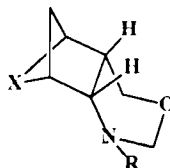
compound **334** was found to be a 93:7 mixture of the *N-in* (**334a**) and *N-out* (**334b**) conformations, respectively, although the H-2 region of the  $^1\text{H}$  spectrum was too complicated at low temperatures to allow the CH–NH coupling to be observed.

Similarly, *cis*-decahydro-3-methylquinazoline (88T1465) was found to be a 92:8 mixture ( $\Delta G^\circ$  4.6 kJ mol $^{-1}$ ) of the *N-in* (**335a**;  $^2J_{2e2a} = -11.0$  Hz) [cf. 71JCS(C)2502; 74JCS(P1)2313]] and *N-out* forms (**335b**;  $^2J_{2e2a} = -10.0$  Hz) [cf. 71JCS(C)2502; 74JCS(P1)2313]], a result that is in accordance with the situation in **333**. The observation of additional couplings of ca. 11 Hz due to  $^3J_{\text{HCNH}}$  in the signals of both H-2a and H-8a pointed to an axial *N*(1)-H and an equatorial *N*-methyl in **335a**. The preferred conformation of *cis*-decahydro-2,3-dimethylquinazoline was in turn confirmed to be **338** (88T1465).

**338**

The  $^1\text{H}$  NMR splitting patterns of the cations of 1- and 3-methyl-*trans*-2-amino-3,4,4a,5,6,7,8,8a-octahydroquinazoline are similar to those of the unmethylated amine [71JCS(C)238] and are consistent with the anancomeric chair–chair conformation. The *cis*-2-aminooctahydroquinazolinium cations behaved like the *cis*-perhydroquinazolinium cations and the *cis*-perhydroquinazolin-2-ones in solution [74JCS(P2)2313]. The 3-methyl derivative assumes only the *N-in* form, whereas the preferred conformation of the 1-methyl and 1,3-dimethyl derivatives is the *N-out* form.

A careful analysis of the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectral parameters (H,H coupling constants and shielding effects) established that the predominant conformation of the hetero ring for *diexo*-deca- and *diexo*-1,2,3,4,4a,5,8,8a-octahydro-5,8-methano-3,1-benzoxazines is the *endo*-boat **339A**, whereas that for the corresponding *diendo* derivatives is the *exo*-boat **339B** (85T5159).

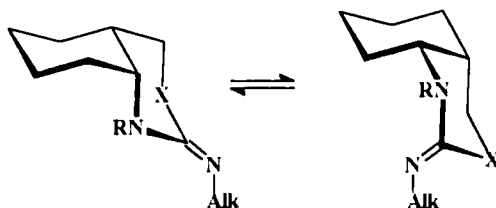
**339A****339B**

X = CH $_2$ CH $_2$  or CH=CH

## 2. Perhydro Derivatives with an $sp^2$ Carbon at Position 2

a. *2-N-Alkylimino*octahydro-2*H*-3,1-benzoxazines and -Thiazines. These derivatives also assume chair–chair conformations in which the carbonyl end is flattened as in cyclohexanones. The *trans*-fused isomers are anancomeric (cf. **330T**), but the *cis*-fused isomers have two interconverting conformations (*Z-in* and *Z-out* forms; cf. **330C**), of which one or the other may predominate (85T5981; 87M503; 90T6859; 93MI2).

The conformations of 2-*N*-methylimino-*cis*- and -*trans*-octahydro-2*H*-3,1-oxazines and -thiazines and their 1-methyl and 1-benzyl derivatives were solved via the  $^1\text{H}$  NMR spectra at ambient (vicinal H,H coupling constants) and low temperatures (integration). 2-*N*-Methylimino-*cis*-octahydro-2*H*-3,1-benzoxazine **340a** was found to be a 62:38 and a 70:30 ( $\Delta G^\circ = 1.2 \text{ kJ mol}^{-1}$ ) mixture of the *N-in* and *N-out* forms at 298 and 173 K, respectively (93MI2). The 1-methyl and 1-benzyl derivatives of **340** are in turn 12:88 and 9:91 mixtures of the *N-in* and *N-out* conformations, which indicates the preference for an axial *N*-substituent in the latter, since the *N-out* form is more favorable in this respect (cf. 96MRC(ip)). The same situation prevails in the corresponding set of 2-*N*-ethyliminooctahydro-2*H*-3,1-benzoxazines (the *N-in* form is preferred by the parent compound and the *N-out* form by its 1-methyl and 1-benzyl derivatives), although the accuracy of the vicinal coupling constants analyzed at 60 MHz does not allow quantitative estimates (87M503).



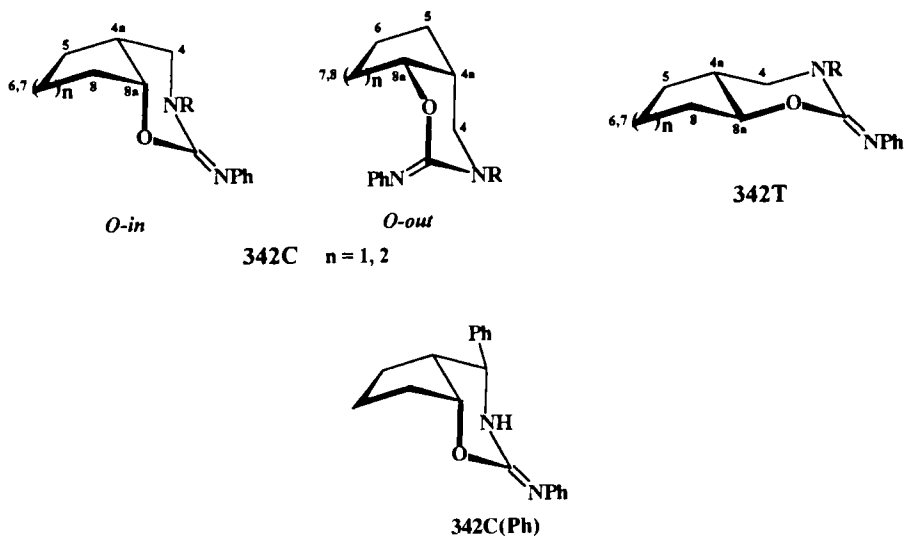
**340:** X = O; **a:** R = H; **b:** R = Me; **c:** R =  $\text{CH}_2\text{Ph}$

**341:** X = S; **a:** R = H; **b:** R = Me; **c:** R =  $\text{CH}_2\text{Ph}$

From the values of the vicinal coupling constants, 2-*N*-methylimino-*cis*-octahydro-2*H*-3,1-benzothiazine **341a** was found to be a 63:37 and a 65:35 ( $\Delta G^\circ = 0.9 \text{ kJ mol}^{-1}$ ) mixture of the *N-in* and *N-out* forms at 298 and 178 K, respectively. Its 1-methyl (**341b**) and 1-benzyl derivatives (**341c**), however, adopt exclusively the *N-out* conformation, as shown by  $J_{4\text{ax},4\text{a}} = \text{ca. } 12.5 \text{ Hz}$  and  $J_{4\text{eq},4\text{a}} = \text{ca. } 4.6 \text{ Hz}$  (93MI2). Again, the approximate coupling data at 60 MHz NMR for the corresponding 2-ethylimino derivatives (87M503) are qualitatively in good agreement with the preceding results and the observed C-13 chemical shifts.

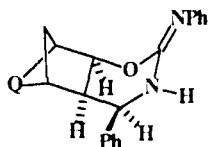
For **340a** and **341a**, another dynamic process was also frozen out. This process must be due to nitrogen inversion in the imino function, which results in *E/Z* isomerization (93MI2). This inversion could occur via amino–imino tautomerism (91JOC3194). The *E* and *Z* isomers are practically equally stable since there is no noteworthy steric hindrance in either form.

b. *2-N-Phenylimino-octahydro-2H-1,3-benzoxazines and -Thiazines and Related Compounds.* A structural study of *cis*- and *trans*-fused 2-phenyliminocyclopent[*e*]oxazine and -octahydro-2*H*-1,3-benzoxazine and their *N*-methyl derivatives has been carried out (85T5981). The *trans*-fused derivatives ( $J_{4ax,4a} = \text{ca. } 11 \text{ Hz}$ ) again assume anancomeric envelope–chair or chair–chair conformations **342T**, whereas the *cis*-fused isomers exist in an equilibrium between the *O-in* [model values for  $J_{4ax,4a} = \text{ca. } 3.4 \text{ Hz}$  and  $J_{4eq,4a} = \text{ca. } 1.4 \text{ Hz}$  from 96MRC998] and the *O-out* envelope–chair or chair–chair conformations **342C** [model values for  $J_{4ax,4a} = \text{ca. } 12.4 \text{ Hz}$  and  $J_{4eq,4a} = \text{ca. } 4.9 \text{ Hz}$  from 96MRC998]. The  $^1\text{H}$  coupling ranges reported for the *cis* isomers (85T5981) contraindicated a conformationally pure system (*O-in* form) and led us to conclude that these compounds involve only ca. 50–65% of the *O-in* conformations. This problem is worthy of further research (as suggested for *cis*-fused isomers in general) since the  $^{13}\text{C}$  NMR chemical shifts of C-6 for the cyclohexane-fused derivatives (85T5981) point to a higher contribution for the *O-in* conformers ( $\geq 80\%$ ).



A *cis*-fused 2-*N*-phenylimino-4-phenylcyclopent[*e*][1,3]oxazine with an equatorial phenyl group **342C** (Ph) was shown by the  $^1\text{H}$  and  $^{13}\text{C}$  NMR data

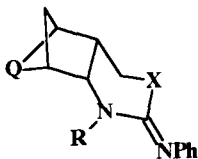
to adopt the *O-in* conformation (90T6859). Similarly, a detailed analysis of the  $^1\text{H}$  and  $^{13}\text{C}$  NMR data (90MRC1045) led to the conclusion that the heterocyclic moiety of 5,8-methano-*r*-4-phenyl-2-phenylimino-*c*-4a,c5,6,7,*c*-8,*c*-8a-hexahydro- **343a** and -*c*-4a,*c*-5,*c*-8,*c*-8a-tetrahydro-4*H*-1,3-benzoxazines **343b** (Ph quasi-equatorial) assumes a boat conformation in



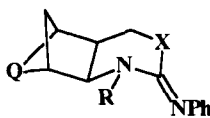
**343a:** Q =  $\text{CH}_2\text{CH}_2$

**343b:** Q =  $\text{CH}=\text{CH}$

which O-1 and C-4 are in the *endo* direction from the plane of the other four atoms, and the dihedral angles of the quasi-equatorial (*exo*) and quasi-axial (*endo*) C-H(4) with C-H(4a) are ca.  $60\text{--}80^\circ$  and ca.  $60\text{--}40^\circ$ . A situation similar to that in **339A** and **339B** (85T5159) prevails in **344**, the heterocyclic part of the *diendo* or *diexo* **344** being in a boat or somewhat twisted boat conformation [87JCS(P1)599; cf. 91JST(246)301].



**344 diendo**

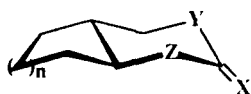


**344 diexo**

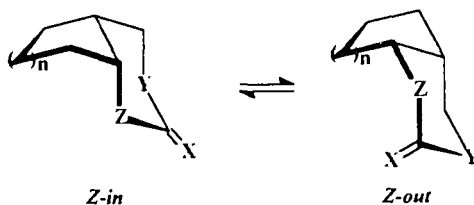
X = O, S; R = H, Me,  $\text{CH}_2\text{Ph}$ ; Q =  $\text{CH}_2\text{CH}_2$ ,  $\text{CH}=\text{CH}$

c. *2-Oxo- and 2-Thioxooctahydro-2H-1,3- and -3,1-Benzoxazines and -Thiazines and Related Compounds.* Several reports deal with the conformations of 2-oxo- and 2-thioxooctahydro-2*H*-1,3- and -3,1-benzoxazines and -thiazines [73OMR159; 82H(19)1191; 83OMR512; 85T1353; 87MRC584] and related cyclopentane- [83T1829] and cycloheptane-fused derivatives (73T981). The *trans*-fused derivatives **345T** assume the anancomeric double-chair conformations, as proved by their  $^1\text{H}$  (chemical shifts and vicinal H,H coupling constants) and  $^{13}\text{C}$  (chemical shifts) NMR parameters. The *cis* isomers **345C** are conformational mixtures of the *Z-in* and *Z-out* forms (Z = O, S, NR), the equilibrium state varying from a clear predominance of the former to one of the latter, as already explained, for example, for 2-*N*-alkyl- and 2-*N*-phenylimino derivatives.

Taking the model values for the vicinal coupling constants of the *O-in*/*N-in* and *O-out*/*N-out* forms as  $J_{4\text{ax},4\text{a}} = \text{ca. } 3.4/2.6 \text{ Hz}$  and  $J_{4\text{eq},4\text{a}} = \text{ca.}$

**345T**

X = O, S; Y = O, S, NR; Z = NR, O, S

**345C**

n = 1, 2, 3

1.4/1 Hz (*Z-in*) and  $J_{4ax,4a} = \text{ca. } 12.4/12.4 \text{ Hz}$  and  $J_{4eq,4a} = \text{ca. } 4.9/4.9 \text{ Hz}$  (*Z-out*) [93MI2; 96MRC(ip)] made it possible to estimate the conformational equilibria for most of the *cis* isomers studied (Table V).

TABLE V  
CONFORMATIONAL EQUILIBRIA IN *cis*-2-Oxo- and -2-Thioxooctahydro-2*H*-1,3-  
and -3,1-Benzoxazines and -thiazines and Related Compounds (**345C**)

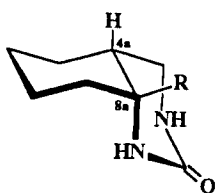
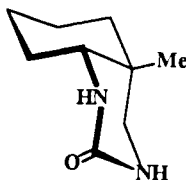
<i>n</i>	Z	Y	X	$\Sigma J$	<i>Z-in/Z-out</i>	Ref.
1	O	NH	O	4	3.2	83T1829 <sup>a</sup>
1	O	NMe	O	5.6	1.6	83T1829 <sup>a</sup>
1	O	NPr <sup>i</sup>	O	5.2	1.9	83T1829 <sup>a</sup>
1	O	NH	S	4	3.2	83T1829 <sup>a</sup>
1	O	NMe	S	5.8	1.4	83T1829 <sup>a</sup>
1	O	NPr <sup>i</sup>	S	5.6	1.6	83T1829 <sup>a</sup>
2	O	NMe	O	4	3.2	73OMR159
2	NH	O	O	2.5	8.1	73OMR159
2	O	NMe	O	6	1.3	82H(19)1191
2	O	NH	S	5	2.0	82H(19)1191
2	O	NMe	S	6	1.3	82H(19)1191
2	NMe	O	S	10	0.16	82H(19)1191
3	O	NH	O	5	2.0	73T981
3	NH	O	O	6.5	0.96	73T981
3	NH	O	O	4.5	2.1	85T1353 <sup>b</sup>
3	NH	O	S	5.0	1.6	85T1353 <sup>b</sup>

<sup>a</sup> The model values selected from cyclohexane-fused compounds may give somewhat overestimated contributions to the *Z-out* conformation in cyclopent[*e*][1,3]oxazines and -thiazines.

<sup>b</sup> 2-Oxo- and 2-thioxo-2*H*-5,6-dihydro-3,1-benzoxazines, respectively.

The heterocyclic moiety of the *diendo*- and *diexo*-fused 2-oxo- and 2-thioxooctahydro- and -1,4,4a,5,8,8a-hexahydro-5,8-methano-3,1- and -1,3-benzoxazines assumes the *exo*- or *endo*-boat conformation, respectively (or a somewhat twisted-boat form, cf. **344**), as concluded from the  $^1\text{H}$  and  $^{13}\text{C}$  NMR data, in agreement with findings reported earlier [85T5159; 87JCS(P2)599; cf. 91JST(246)301].

Several 8a-substituted *cis*-octahydroquinazolin-2(1*H*)-ones **346C** clearly prefer the *N(1)-in* chair-chair conformation [71JCS(C)1812], as confirmed by the small values of the two  $J_{\text{H-4a,H-8a}}$  coupling constants (2–4 Hz). Similar small values were found for both  $J_{\text{H-4,H-3}}$  couplings of 4a-methyl-*cis*-octahydroquinazolin-2(1*H*)-one. This can be explained by either an *N(1)-in* or an *N(2)-out* conformation [N(3)-H equatorial], but the latter (**347C**) appears to be more probable because the 1,3-diaxial Me,NH interactions are less severe than Me,CH<sub>2</sub> interactions (Table IV).

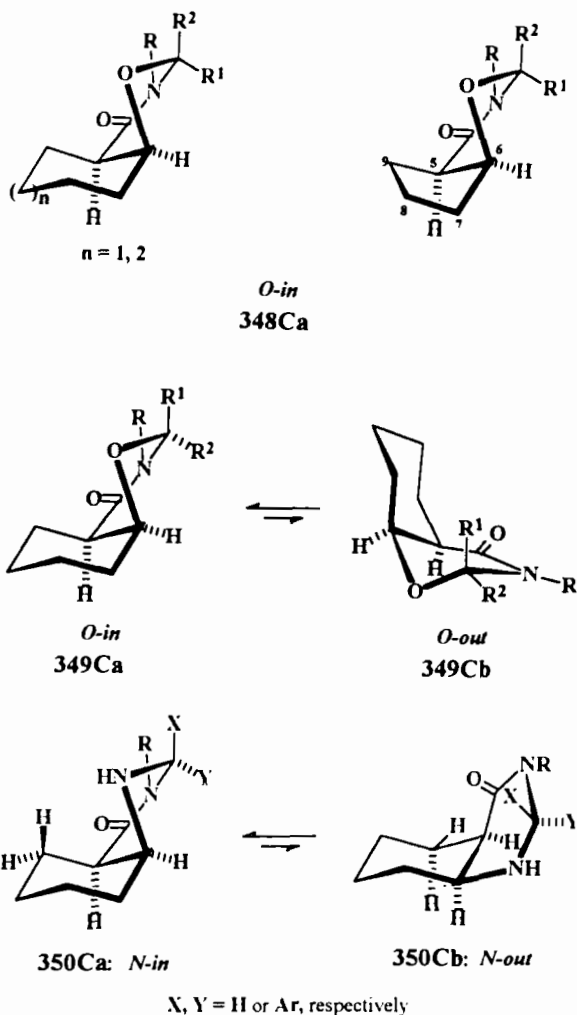
**346C****347C**

### 3. *Perhydro Derivatives with an $sp^2$ Carbon at Position 4*

The general principle that the protons in the alicyclic six-membered rings of saturated six-five-, six-six-, and six-seven-membered fused ring systems give the smallest  $\Sigma J$  values (ca. 8–11 Hz) for 4a- and 8a-H in the *Z-in* form, intermediate values (ca. 20 Hz) in the *Z-out* form for the *cis*-fused isomers, and clearly higher  $\Sigma J$  values (ca. 25–30 Hz) for the *trans*-fused isomers [71JCS(C)3222] is applied next to estimate the conformational equilibria in 4-oxo-(thioxo) and 2,4-dioxo(thioxo) derivatives.

All perhydro derivatives with an  $sp^2$  carbon at position 4 prefer conformations in which the heterocyclic moiety exists in a half-chair form (**348T**–**350T** and **348C**–**350C**).  $\Sigma J(\text{H-8a})$  in the  $^1\text{H}$  spectrum is a suitable indicator of the conformational status in these cases.

In the anancomeric *trans* isomers, the coupling pattern of H-8a consists of two diaxial couplings (ca. 11 Hz each) and one axial,equatorial coupling (ca. 4 Hz). Thus,  $\Sigma J(\text{8a-H}) = 25\text{--}30\text{ Hz}$  [84JCS(P1)2043; 87T4731; 92T4963]. In the *cis* isomers [84JCS(P1)2043; 87T4565, 87T4731; 92T4963], the heterocyclic moiety also adopts a half-chair form, but the limiting value for  $\Sigma J(\text{8a-H})$  is a sum of e,e- and e,a-type couplings (model values for the *Z-in*

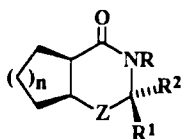


form of ca. 8 Hz for cyclohexane- and cycloheptane-fused derivatives [84JCS(P1)2043; 87T4565] and ca. 10.5 Hz for cyclopentane-fused derivatives [87T4565]) or that of two e,a- and one a,a-type couplings (model value for the *Z-out* form of ca. 20 Hz [84JCS(P1)2043]), that is, clearly smaller than for the *trans* isomers in both cases. When Z = O, the *O-in* conformation (**348Ca–350Ca**) is strongly favored (Table VI), the *Z-out* conformation (**349Cb–350Cb**) making a fairly minor contribution, except in the cycloheptane-fused derivatives [84JCS(P1)2043], where it is practically exclusive (Table VI). In the octahydroquinazolin-4-ones, the *N-out* form is much more feasible (Table VI).



TABLE VI

CONFORMATIONAL EQUILIBRIA IN SEVERAL *cis*-FUSED HEXAHYDROCYCLOPENT[*e*][1,3]OXAZIN-4-ONES ( $n = 1$ ), HEXAHYDRO-2*H*-1,3-BENZOXAZIN-4-ONES ( $n = 2$ ), OCTAHYDROCYCLOHEPT[*e*][1,3]OXAZIN-4-ONES ( $n = 3$ ) AND OCTAHYDROQUINAZOLIN-4-ONES ( $n = 2$ )



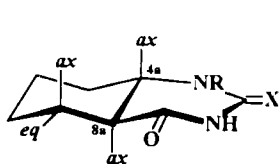
<i>n</i>	Z	R	R <sup>1</sup>	R <sup>2</sup>	Σ <i>J</i> (8a-H)	% of <i>Z</i> -in	Ref.
1	O	H	Ar <sup>a</sup>	H	10	<i>O</i> -in	84JCS(P1)2043
2	O	H	Ar <sup>a</sup>	H	8	<i>O</i> -in	84JCS(P1)2043
3	O	H	Ar <sup>a</sup>	H	20	<i>O</i> -out	84JCS(P1)2043
1	O	Me	Ar <sup>a</sup>	H	8	84% <i>O</i> -in	84JCS(P1)2043
2	O	Me	H	H	8	<i>O</i> -in	84JCS(P1)2043
3	O	Me	Ar <sup>a</sup>	H	20	<i>O</i> -out	84JCS(P1)2043
1	O	H	Me	Et	10.8	<i>O</i> -in	87T4565
1	O	H	Me	Pr <sup>i</sup>	10.4	<i>O</i> -in	87T4565
1	O	H	Me	<i>t</i> -Bu	10.3	<i>O</i> -in	87T4565
1	O	H	Me	Ph	11.4	90% <i>O</i> -in	87T4565
1	O	H	Et	Me	10.8	97% <i>O</i> -in	87T4565
1	O	H	Pr <sup>i</sup>	Me	10.5	<i>O</i> -in	87T4565
1	O	H	Ph	Me	13.0	74% <i>O</i> -in	87T4565
2	O	H	Me	Et	8.2	<i>O</i> -in	87T4565
2	O	H	Me	Pr <sup>i</sup>	~8	<i>O</i> -in	87T4565
2	O	H	Me	<i>t</i> -Bu	8.5	<i>O</i> -in	87T4565
2	O	H	Me	Ph	~9	~90% <i>O</i> -in	87T4565
2	O	H	Et	Me	8.5	<i>O</i> -in	87T4565
2	O	H	Pr <sup>i</sup>	Me	~8	<i>O</i> -in	87T4565
2	O	H	Ph	Me	~9	92% <i>O</i> -in	87T4565
<i>n</i>	Z	R	(R <sup>1</sup> = R <sup>2</sup> = H)				
1	O	CH <sub>2</sub> OH			12.8	76% <i>O</i> -in	92T4963
2	O	CH <sub>2</sub> OH			9.7	86% <i>O</i> -in	92T4963
1	O	H			13.6	67% <i>O</i> -in	92T4963
2	O	H			<8.7	>94% <i>O</i> -in	92T4963
2	O	CONHPh			11.3	72% <i>O</i> -in	92T4963
1	O	OCONHPh			14.0	63% <i>O</i> -in	92T4963
2	O	OCONHPh			8.9	92% <i>O</i> -in	92T4963
<i>n</i>	Z	R	R <sup>1</sup>	R <sup>2</sup>			
2	N	H	Ar <sup>a</sup>	H	10.5	79% <i>N</i> -in	87T4731
2	N	Me	Ar <sup>a</sup>	H	10.5	79% <i>N</i> -in	87T4731
2	N	H	H	Ar <sup>a</sup>	16.3	31% <i>N</i> -in	87T4731
2	N	Me	H	Ar <sup>a</sup>	14.0	50% <i>N</i> -in	87T4731

<sup>a</sup> *p*-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>.

#### 4. Perhydro Derivatives with $sp^2$ Carbons at Positions 2 and 4

In these compounds, too, the best conformational indicator is  $\Sigma J(8a-H)$ . The most probable conformation of the heterocyclic moiety is a sofa (or slightly distorted sofa) form, where the  $N-C(=O)-N-C(=O)$  grouping is (nearly) coplanar. Again the *trans*-fused derivatives are easy to distinguish, because of their large  $\Sigma J(8a-H)$  value of 25–30 Hz [69T3807; 85ACH(118)71]. The limiting values for the *Z-in* and *Z-out* conformations of the *cis*-fused derivatives are ca. 8 and 20 Hz, respectively [69T3807, cf. Section III,B,3].

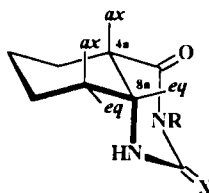
Accordingly, the *trans*-fused 2,4-dioxodecahydroquinazoline **351T** has a biased chair–sofa conformation, whereas the *cis* isomer consists of an approximately 61:39 conformational mixture of the *N(I)-out* and *N(I)-in* forms (**351C**), in agreement with an early estimate (69T3807). In the



$$\Sigma J(8a-H) = 2J_{aa} + J_{ae}$$

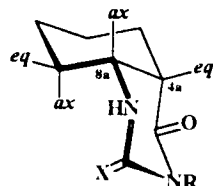
**351T**

R = H or Ar; X = O or S



$$\Sigma J(8a-H) = 2J_{ea} + J_{ee}$$

*N-in*



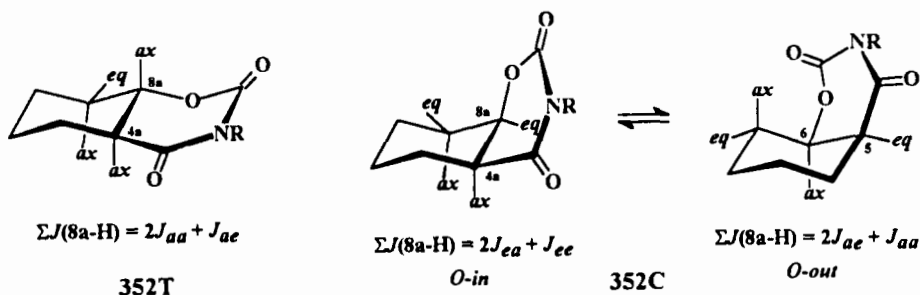
$$\Sigma J(8a-H) = 2J_{ae} + J_{aa}$$

**351C**

*N-out*

cases of the *cis*-fused 3-aryl-2,4-dioxooctahydro-1*H*-cyclopentapyrimidine and -decahydroquinazoline (Ar = Ph, *m*- and *p*-ClC<sub>6</sub>H<sub>4</sub>), the values reported for  $\Sigma J(8a-H)$  [or  $\Sigma J(4a-H)$ ], which are 20 [25] and 20 [10] Hz, respectively, are not logical (see also Section III,B,3) in light of the limiting values [*trans*:  $\Sigma J(8a-H) = \Sigma J(4a-H) = 2J_{aa} + J_{ae} = 25\text{--}30$  Hz (cf. **351T**) and *cis*: *N-in*  $\Sigma J(8a-H) = 2J_{ea} + J_{ee} = \text{ca. } 8$  and  $\Sigma J(4a-H) = 2J_{ae} + J_{aa} = 20$  Hz, and *N-out*  $\Sigma J(8a-H) = 2J_{ae} + J_{aa} = 20$  Hz and  $\Sigma J(4a-H) = 2J_{ea} + J_{ee} = 8$  Hz (cf. **351C**)]. Hence, their <sup>1</sup>H spectra and conformational status should be revisited, although the preceding result for **351C** (R = H) (69T3807) allows one to postulate that, when R = *m*- or *p*-ClC<sub>6</sub>H<sub>4</sub>, **351C** likewise contains appreciable amounts of both *N-in* and *N-out* forms.

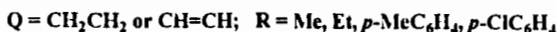
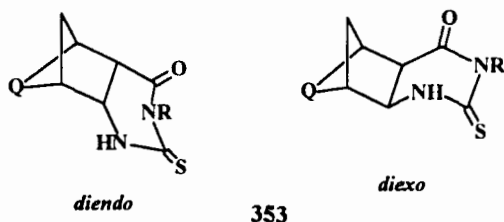
It must be emphasized that the value of 25 Hz given for  $\Sigma J(H-4a)$  of *N*-substituted *cis*-fused 2,4-dioxo-5,6,7,7a-tetrahydrocyclopent[*e*][1,3]oxazin-4-ones and -4a,5,6,7,8,8a-hexahydro-2*H*-1,3-benzoxazines (**352C**) cannot be correct. As stated previously (cf. also Section III,B,3), this value is ca. 8–10 Hz for the *O-in* and ca. 20 Hz for the *O-out* conformation. In all cases studied (85M857), the value of  $\Sigma J(4a-H)$  is 12 Hz, which would suggest a



2:1 ratio for the *O-in* and *O-out* forms (cf. **352C**). Although the C-13 chemical shifts are in qualitative agreement with the latter suggestion, at least the  $^1\text{H}$  NMR analyses should be reconsidered [85M857].

The *trans*-fused 3-methyl- and 2-phenyl-substituted 4-oxo-4a,5,6,7,8,8a-hexahydroquinazoline- and -4-oxo-4a,5,8,8a-tetrahydroquinazoline-2 (1*H*)-thiones (**351T**,  $\text{X} = \text{S}$ ) exhibit normal biased chair-sofa [ $\Sigma J(8a-H) = 24 \text{ Hz}$ ] and half-chair-sofa [ $\Sigma J(4a-H) = \Sigma J(8a-H) = 30 \text{ Hz}$ ] conformations, respectively [85ACH(118)71]. The *cis* isomers (**351C**,  $\text{X} = \text{S}$ ) comprise practically equimolar mixtures of *N-in* and *N-out* chair-sofa and half-chair-sofa forms, as concluded from the fact that  $\Sigma J(4a-H) = \Sigma J(8a-H) = 16 \text{ Hz}$  (suggesting limiting values of 8/24 or 10/22 Hz). The similarity of the C-5 and C-7 chemical shifts (average  $\gamma$ -effects) supports the above postulation [85ACH(118)71].

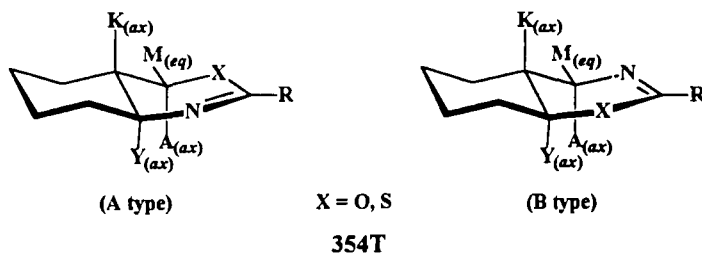
In accordance with the  $^1\text{H}$  and  $^{13}\text{C}$  NMR parameters, the heterocyclic moiety of the *N*-substituted ( $\text{R} = \text{Me}, \text{Et}, \text{Ph}, p\text{-MeC}_6\text{H}_4, p\text{-ClC}_6\text{H}_4$ ) *diendo*- and *diexo*-fused 4-oxo-4a,5,6,7,8,8a-hexahydro-1*H*- and -4a,5,8,8a-tetrahydro-1*H*-5,8-methanoquinazoline-2-thiones **353** assumes a distorted sofa conformation in which the  $\text{N}(1)-\text{C}(=\text{S})-\text{N}(3)$  grouping forms the tip of the sofa [85JCS(P1)2483].



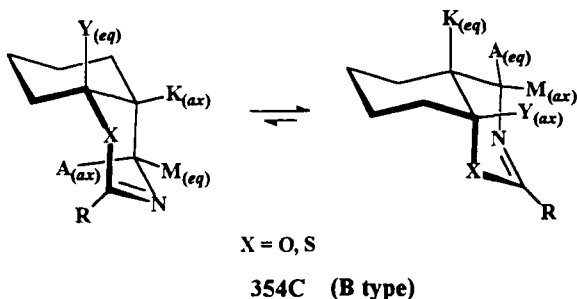
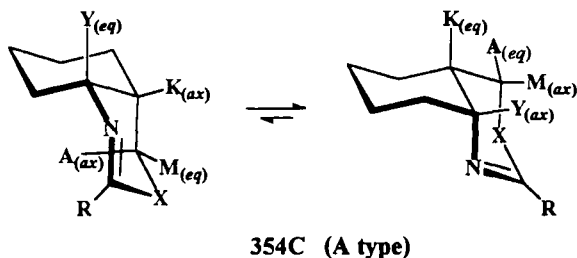
## 5. Dihydro Derivatives

*a. Dihydrooxazines and Dihydrothiazines Fused with Five- to Eight-Membered Cycloalkanes.* Since the  $\text{O}-\text{C}=\text{N}-\text{C}$  grouping in 4a,5,6,7,-

8,8a-hexahydro-4*H*-3,1- and -1,3-benzoxazine forms an almost planar delocalized multiple bond system (82CSC1777; 83OMR512, 83T1829; 86MRC145, 86T2345), a chair-half-chair or chair-sofa conformation must be discussed in this context rather than a chair-chair conformation [76H(4)293]. In the case of cyclohexane-fused derivatives, however, the chair-half-chair conformation is in better agreement with the crystallographic data (79T799) and also fits better with the NMR results (84OMR597, 86MRC145, 86T2345. In cyclopentane-, cycloheptane-, and cyclooctane-fused derivatives, the heterocyclic moiety similarly appears to prefer a half-chair form (84OMR597).



The *trans* isomers exist, as usual, in chair-half-chair **354T** or corresponding types of conformations in which the heterocyclic part assumes a half-chair (or sofa) form, as revealed by the characteristic coupling data and  $^{13}\text{C}$  chemical shift data [71JCS(C)238, 79T799; 84OMR597; 86MRC145,



86T2345], whereas the *cis* isomers consist of mixtures of *Z-in* and *Z-out* (*Z* = N, O) conformations **354C** (Table VII). The contributions can in most cases be derived from the vicinal  $J_{HH}$  coupling data for H(4ax) and H(4eq) [A and M] and in a few cases from the  $^{13}\text{C}$  chemical shifts. In almost all cases (Table VII), the *N-* or *O(S)-in* form is present in a somewhat higher amount than the corresponding *N-* or *O(S)-out* chair–half-chair or chair–sofa conformation (this is the case with the respective conformations of cyclopentane-, cycloheptane-, and cyclooctane-fused derivatives, the conformations of the carbocycles usually being envelope, chair, and boat–chair [or crown or chair–chair], respectively [94MI3]).

The conformational status estimated for the *cis* compounds (Table VII) consistently [71JCS(C)238; 79T799; 86MRC145, 86T2345] differs in some cases from other conformational conclusions (79T799; 84OMR597).

The *cis*- and *trans*-2-*p*-chlorophenyl)-4a,5,8,8a-tetrahydro-4*H*-3,1-benzoxazines [85T1353] exhibit values of 5.6 and 10.5 for the *trans* couplings between H(4) and H(4a), respectively, which indicates a (distorted) half-chair–sofa or sofa–half-chair form for the latter and a 56:44 mixture of the corresponding *N-in* and *N-out* forms for the former [limiting *J* values:  $J_{cc} = 1.4$  Hz and  $J_{aa} = 11.0$  Hz (86MRC145)], in agreement with the  $^{13}\text{C}$  NMR data (85T1353).

TABLE VII

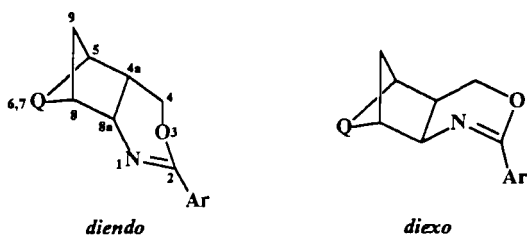
CONFORMATIONAL EQUILIBRIA IN SEVERAL *cis*-FUSED HEXAHYDROCYCLOPENT[*e*][1,3]OXAZINES (*n* = 3, **B**), HEXAHYDRO-2*H*-3,1- (**A**) AND -1,3-BENZOXAZINES (*n* = 4, **B**, **354C**), OCTAHYDROCYCLOHEPT[*d*][1,3]- (**A**) AND [*e*][1,3]OXAZINES (*n* = 5, **B**), AND OCTAHYDRO-2*H*-CYCLOOCTA[*e*][1,3]THIAZINES (*n* = 6, **B**)

Type	<i>n</i>	X	R	Source	% of <i>N-in</i>	% <i>O/S-in</i>	Ref.
<b>A</b>	4	O	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	$J_{HH}$	73		79T799
<b>A</b>	5	O	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	$J_{HH}$	42		79T799
<b>B</b>	4	O	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	$J_{HH}$		83	79T799
<b>B</b>	5	O	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	$J_{HH}$		62	79T799
<b>A</b>	4	O	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	$J_{HH}$	68		86MRC145
<b>A</b>	4	O	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	$\delta$ ( $^{13}\text{C}$ )	69		86MRC145
<b>B</b>	4	O	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	$J_{HH}$		90	86MRC145
<b>B</b>	4	O	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	$\delta$ ( $^{13}\text{C}$ )		93	86MRC145
<b>A</b>	4	O	SCH <sub>3</sub>	$J_{HH}$	68		86T2345
<b>A</b>	4	O	SCH <sub>3</sub>	$\delta$ ( $^{13}\text{C}$ )	73		86T2345
<b>B</b>	4	O	SCH <sub>3</sub>	$J_{HH}$		89	86T2345
<b>B</b>	3	S	Ph	$J_{HH}$		46	84OMR597
<b>B</b>	4	S	Ph	$J_{HH}$		79	84OMR597
<b>B</b>	5	S	Ph	$J_{HH}$		56	84OMR597
<b>B</b>	6	S	Ph	$J_{HH}$		74	84OMR597
<b>B</b>	4	S	NH <sub>2</sub>	$J_{HH}$		70	71JCS(C)238
<b>B</b>	4	O	NH <sub>2</sub>	$J_{HH}$		83	71JCS(C)238

$J_{ee} = 1.4$  Hz and  $J_{aa} = 11.0$  Hz (86MRC145)], in agreement with the  $^{13}\text{C}$  NMR data (85T1353).

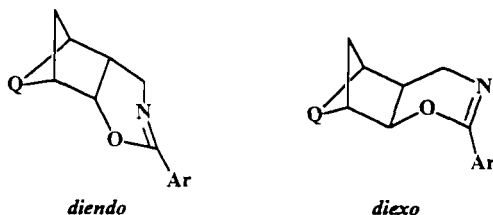
In spite of the presence of two double bonds and a carbonyl group in the fused bicycle, *cis*-2-phenyl-4a,5,8,8a-tetrahydroquinazolin-4(3*H*)-one exists predominantly in the *N-in* form, as indicated by  $\Sigma J(8a\text{-H}) = 10$  Hz (for the *trans* isomer  $>30$  Hz) and the  $^{13}\text{C}$  NMR shift effects (85T1353).

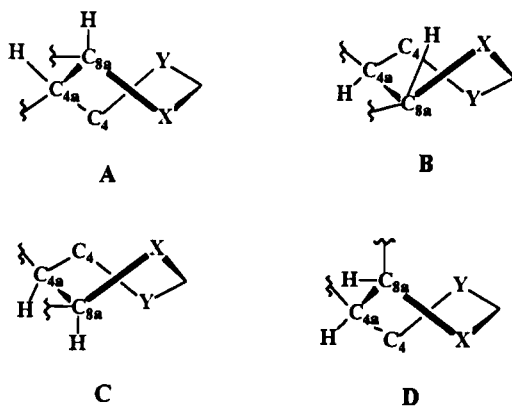
b. *Norbornane- and Norbornene-Fused Dihydro-1,3- and -3,1-Oxazines and Tetra- and Hexahydroquinazolin-4-ones.* Thorough  $^1\text{H}$  and  $^{13}\text{C}$  NMR studies (vicinal H,H coupling constants, shielding and substituent effects) on *diendo*- and *diexo*-2-aryl-4a,5,6,7,8,8a-hexahydro- and 4a,5,6,8a-tetrahydro-5,8-methano-4*H*-3,1- and -1,3-benzoxazines **355** [83OMR512; 87MRC584] revealed that the *diendo* compounds prefer a boat (or somewhat distorted boat, **356A**) conformation where the hetero atom at position 3 (X) is *exo*-tilted relative to the alicyclic skeleton, whereas **356C** with *exo*-C-4 is preferred in the *diexo* series, as reported for related systems [85T5159; 87JCS(P2)599; 90MRC1045]. Similar conformational conclusions prevail for the oxazine moiety of tetracyclic fused-skeleton compounds **357a–357d** [87MRC635; 91MRC706] and for the heterocyclic rings in *diendo*- and *diexo*-4a,5,6,7,8,8a-hexahydro- and 4a,5,6,8a-tetrahydro-3*H*-5,8-methanoquinazolin-4-ones **358** (87CB259).

**355**

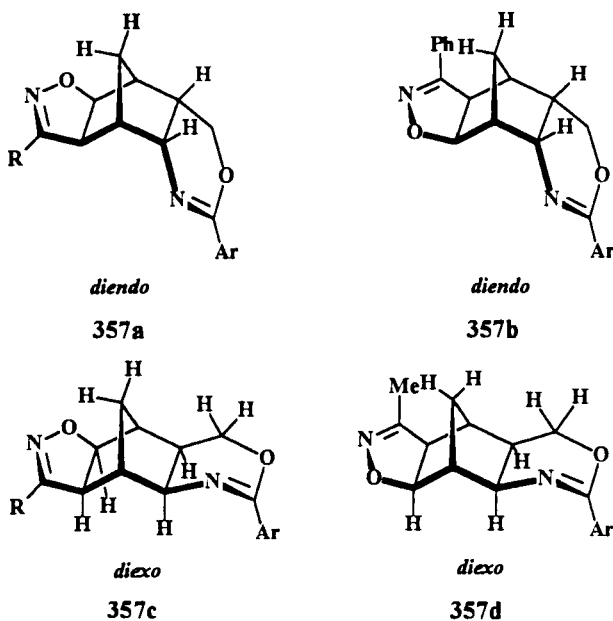
**a:** Ar = *p*-ClC<sub>6</sub>H<sub>4</sub>; **b:** Ar = *m*-ClC<sub>6</sub>H<sub>4</sub>; **c:** Ar = *p*-MeC<sub>6</sub>H<sub>4</sub>; **d:** Ar = C<sub>6</sub>H<sub>5</sub>

Q = CH<sub>2</sub>CH<sub>2</sub>, CH=CH



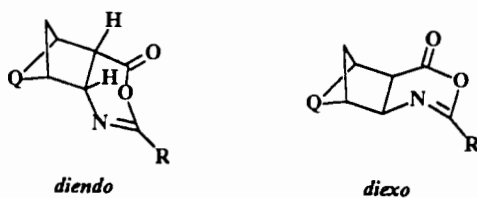


356

R = Me, Ph; Ar = *p*-ClC<sub>6</sub>H<sub>4</sub>

## 6. X-Ray Results Showing Perspective Views of Alicycle-Fused 1,3-Oxazines, 1,3-Thiazines, and Pyrimidines

Here, perspective views of the structures determined by X-ray diffraction and Newmann projections are presented, together with the names given



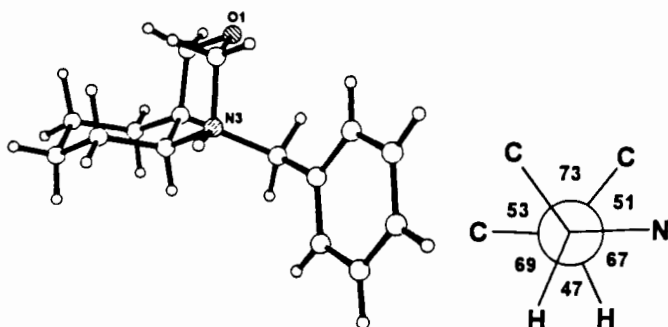
358

R = C<sub>6</sub>H<sub>5</sub>, *p*-ClC<sub>6</sub>H<sub>4</sub>, *m*-ClC<sub>6</sub>H<sub>4</sub>, *p*-MeC<sub>6</sub>H<sub>4</sub>, cyclohexyl  
 Q = CH<sub>2</sub>CH<sub>2</sub> or CH=CH

by *Chemical Abstracts*, and the references. The data were collected from the Cambridge Crystallographic Data Centre. The perspective views are such that in the *cis* derivatives the annelational hydrogens are  $\alpha,\alpha$ , whereas in the *trans* derivatives the annelational hydrogen next to the heteroatom is  $\alpha$ . The Newmann projections are given for annelational carbons. If symmetry-independent molecules were found in the solid state, both structures are given. (Thanks for the data collection are due to Dr. Gyula Argay, Central Research Institute of Chemistry, Hungarian Academy of Science, Budapest.)

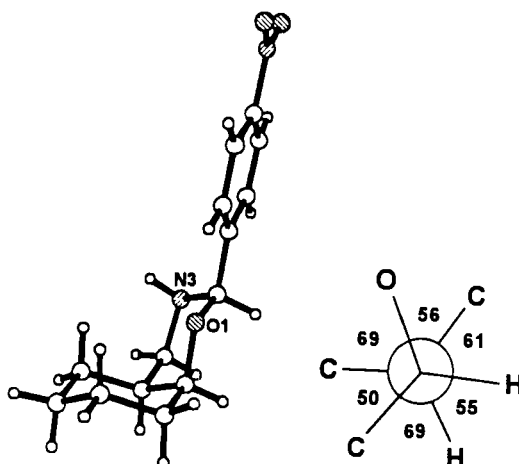
#### a. Oxazine Derivatives

*cis*-Octahydro-1-phenylmethyl-2*H*-3,1-benzoxazine (84T2053)

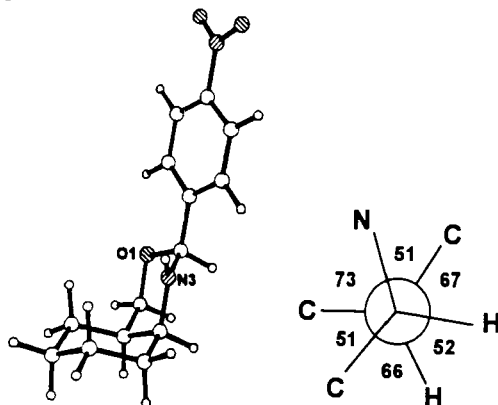




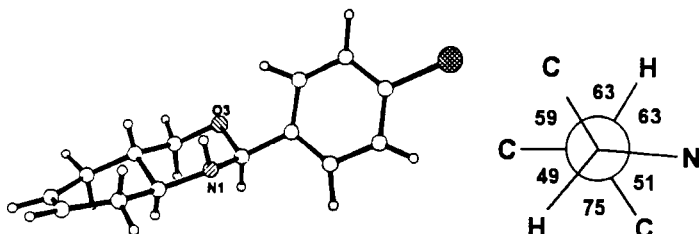
(2 $\alpha$ ,4 $\alpha\beta$ ,8 $\alpha\beta$ )-Octahydro-2-(4-nitrophenyl)-2*H*-1,3-benzoxazine  
[82ACH(109)39]



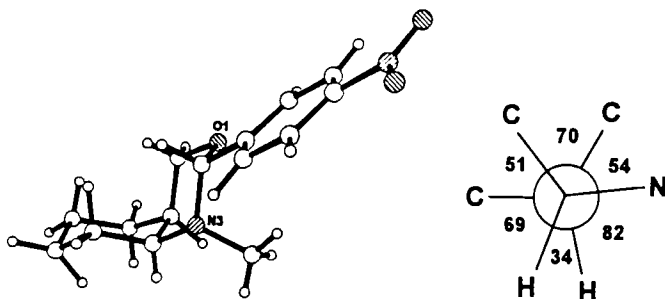
(2 $\alpha$ ,4 $\alpha\alpha$ ,8 $\alpha\beta$ )-Octahydro-2-(4-nitrophenyl)-2*H*-3,1-benzoxazine  
[82ACH(109)39]



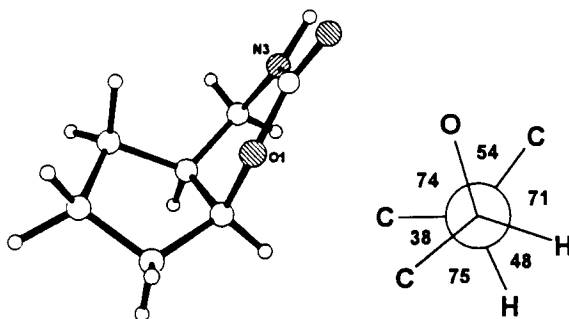
(2 $\alpha$ ,4 $\alpha\alpha$ ,8 $\alpha\beta$ )-2-(4-Chlorophenyl)-1,4,4 $\alpha$ ,5,8,8 $\alpha$ -hexahydro-2*H*-3,1-benzoxazine [86AX(C)1884]



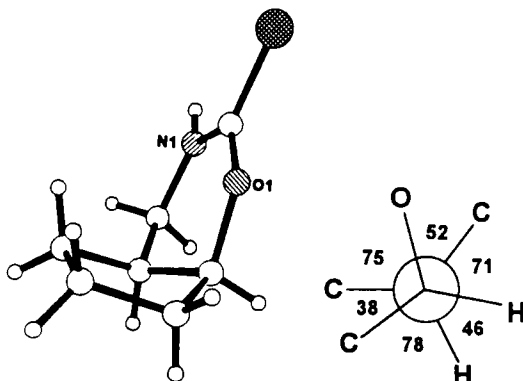
(2 $\alpha$ ,4 $\alpha\beta$ ,8 $\alpha\beta$ )-Octahydro-1-methyl-2-(4-nitrophenyl)-2*H*-3,1-benzoxazine (84T3587)

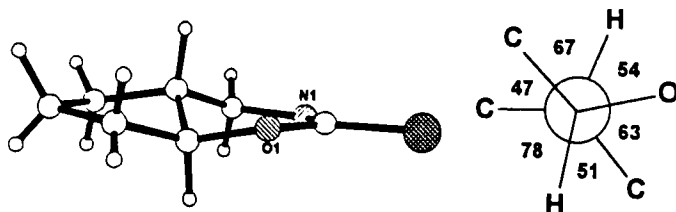
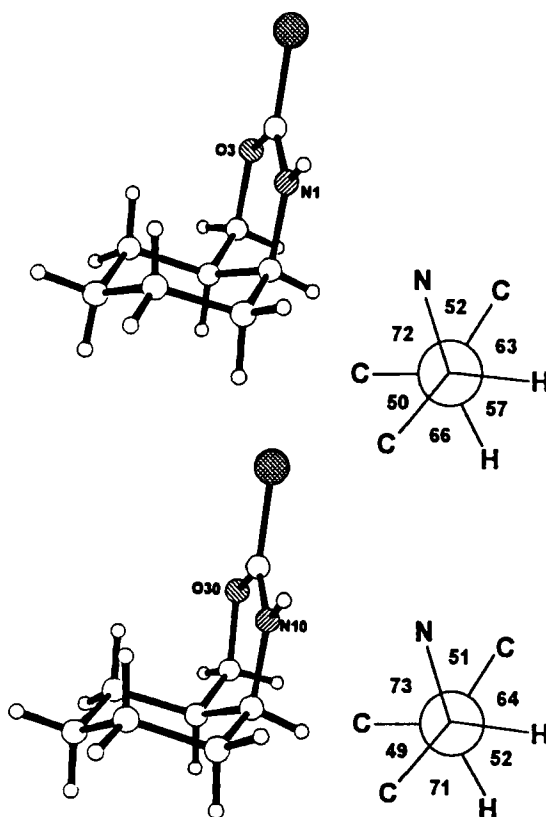


*cis*-Hexahydrocyclopent[*e*][1,3]oxazin-2(3*H*)-one [85JST(131)45]

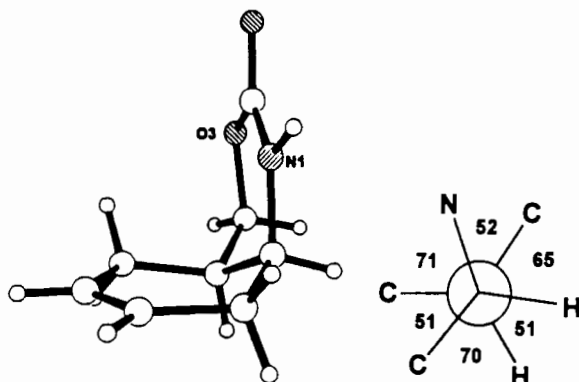


*cis*-Hexahydrocyclopent[*e*][1,3]oxazine-2(3*H*)-thione [85JST(131)45]

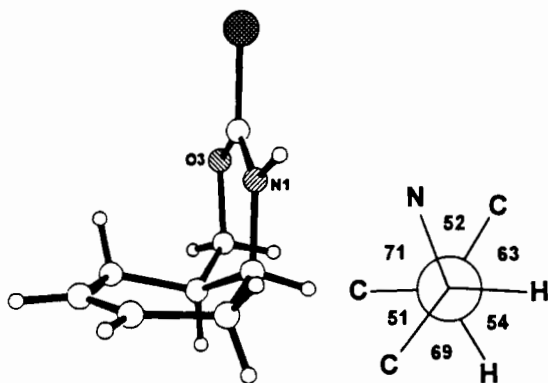


*trans*-Hexahydrocyclopent[*e*][1,3]oxazine-2(3*H*)-thione (83T1829)*cis*-Octahydro-2*H*-3,1-benzoxazine-2-thione [85JST(131)31]

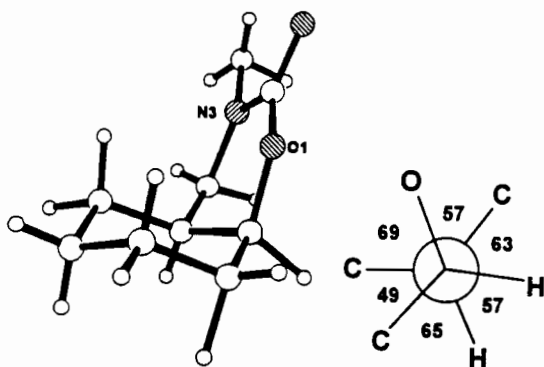
*cis*-1,4,4a,5,8,8a-Hexahydro-2*H*-3,1-benzoxazin-2-one [85JST(131)31]

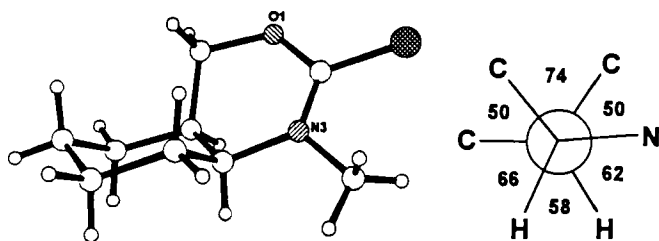
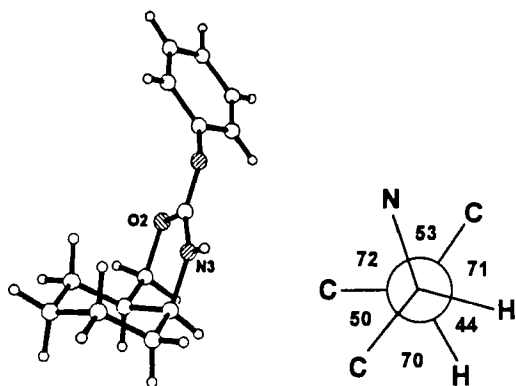
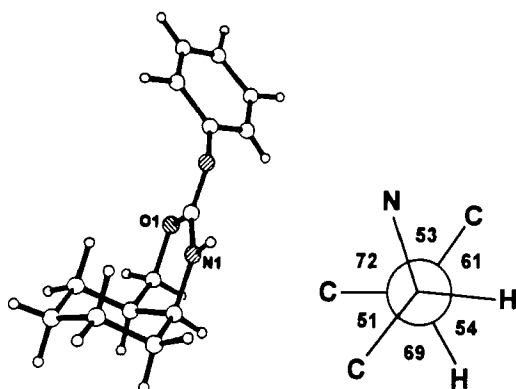


*cis*-1,4,4a,5,8,8a-Hexahydro-2*H*-3,1-benzoxazine-2-thione [85JST(131)31]

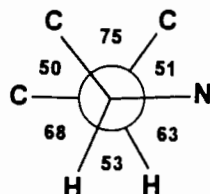
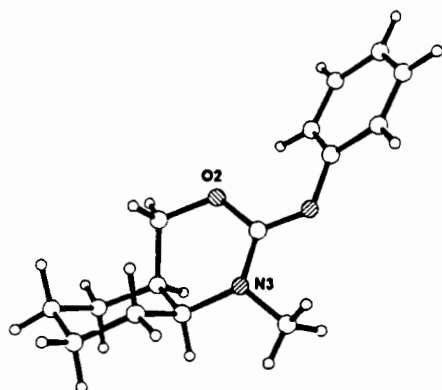
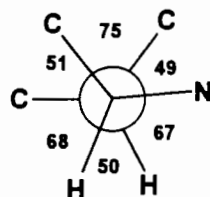
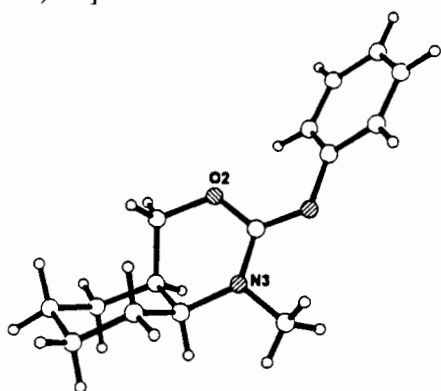


*cis*-Octahydro-3-methyl-2*H*-1,3-benzoxazin-2-one [85JST(131)45]

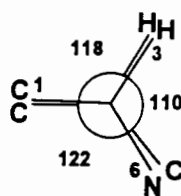
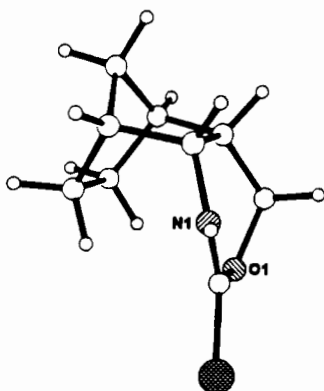


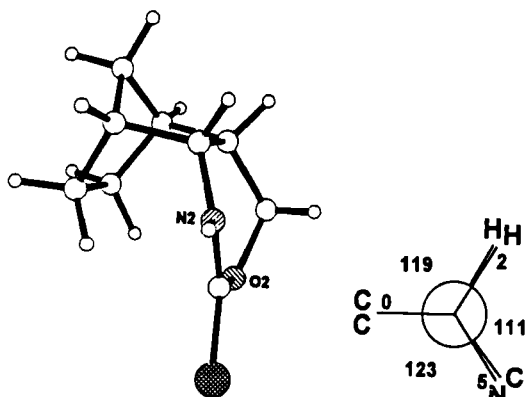
*cis*-Octahydro-1-methyl-2*H*-3,1-benzoxazine-2-thione (82CSC1777)*cis*-4a,5,6,7,8,8a-Hexahydro-*N*-phenyl-4*H*-3,1-benzoxazine-2-amine [87JST(161)125]

*cis-N*-(Octahydro-1-methyl-2*H*-3,1-benzoxazin-2-ylidene)benzeneamine  
[87JST(161)125]

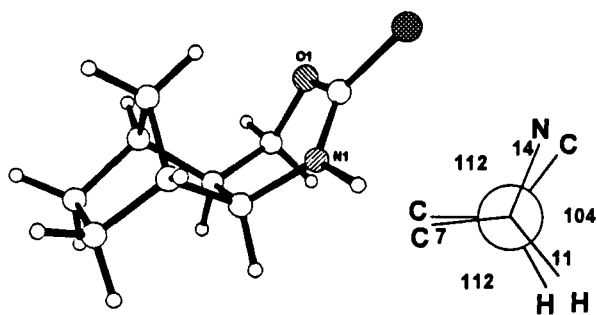


(4 $\alpha$ ,5 $\beta$ ,8 $\beta$ ,8 $\alpha$ )-Octahydro-5,8-methano-2*H*-3,1-benzoxazine-2-thione  
[90AX(C)1495]

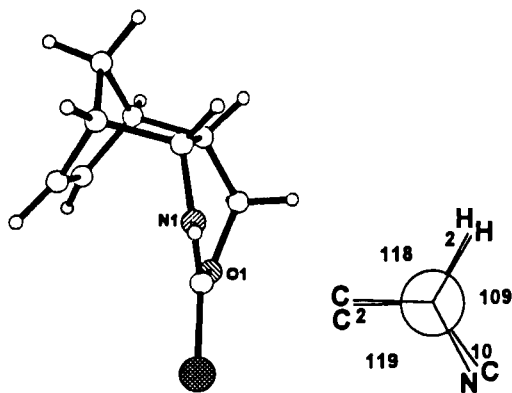


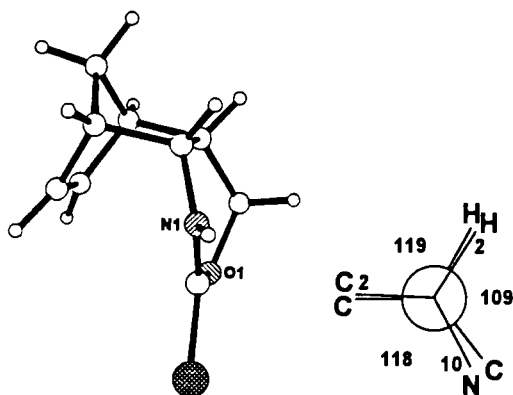


(4 $\alpha$ ,5 $\alpha$ ,8 $\alpha$ ,8 $\alpha$ )-Octahydro-5,8-methano-2*H*-3,1-benzoxazine-2-thione  
[90AX(C)1495]

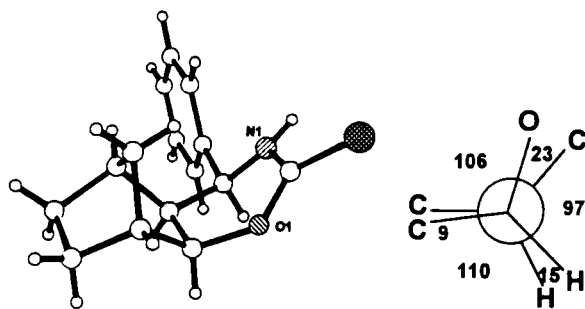


(4 $\alpha$ ,5 $\alpha$ ,8 $\alpha$ ,8 $\alpha$ )-1,4,4*a*,5,8,8*a*-Hexahydro-5,8-methano-2*H*-3,1-benzoxazine-2-thione [87AX(C)1347]

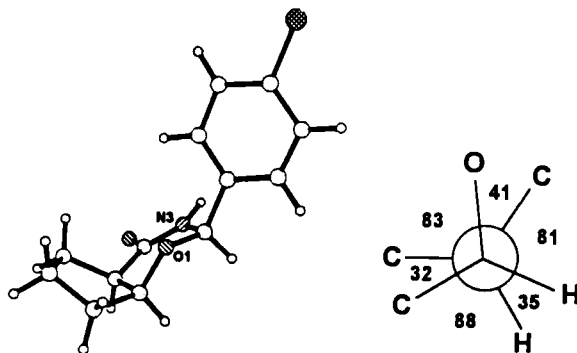




(4 $\alpha$ ,4a $\beta$ ,5 $\alpha$ ,8 $\alpha$ ,8a $\beta$ )-Octahydro-4-phenyl-5,8-methano-2H-3,1-benzoxazine-2-thione [91JST(248)167]

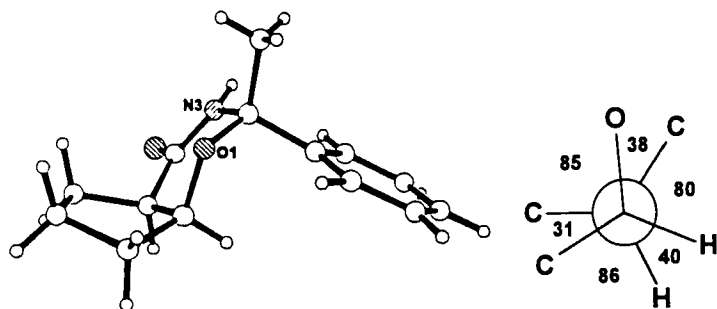


(2 $\alpha$ ,4a $\beta$ ,7a $\beta$ )-2-(4-Chlorophenyl)hexahydrocyclopent[e][1,3]oxazin-4(4H)-one (80CSC335)

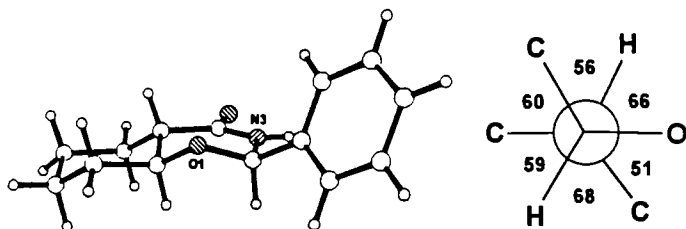




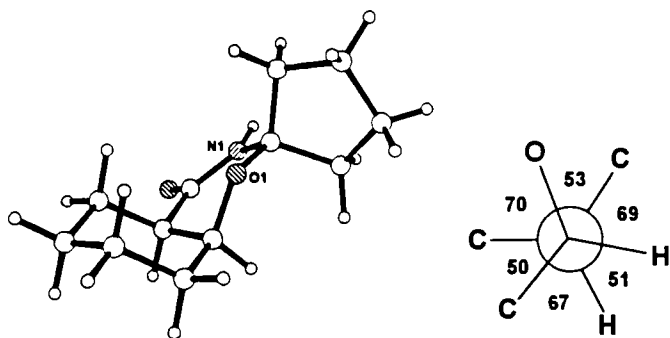
(2 $\alpha$ ,4 $\alpha$ ,7 $\alpha$ )-Hexahydro-2-methyl-2-phenylcyclopent[*e*][1,3]oxazin-4(4*H*)-one (82CSC959).



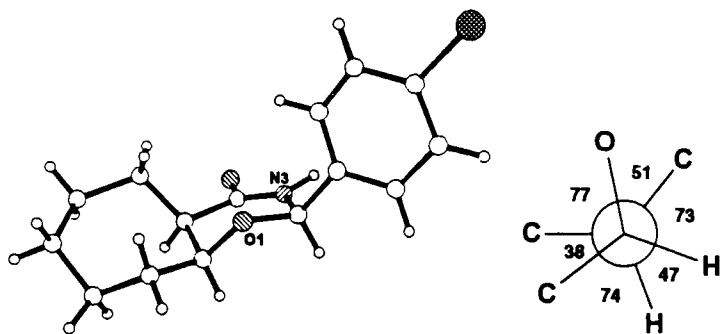
(2 $\alpha$ ,4 $\alpha$ ,8 $\alpha$ )-Octahydro-2-phenyl-4*H*-1,3-benzoxazin-4-one  
[85ACH(118)103]



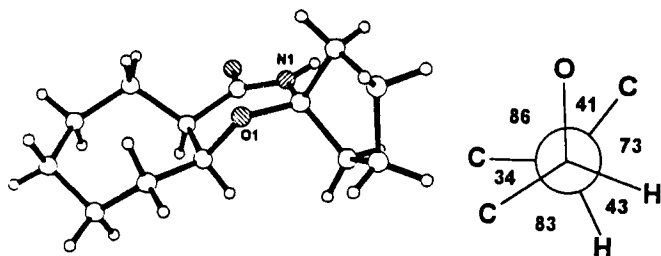
*cis*-Hexahydrospiro[2*H*-1,3-benzoxazine-2,1'-cyclopentan]-4(3*H*)-one  
[89JST(192)125]



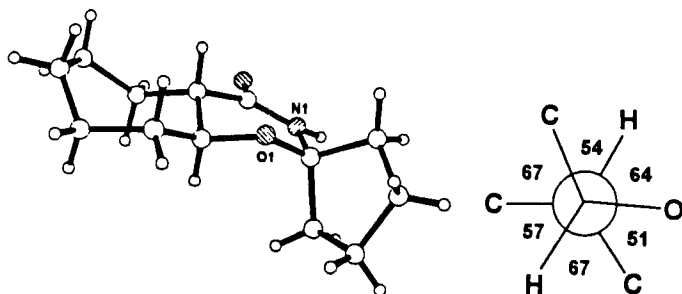
(2 $\alpha$ ,4 $\alpha$ ,9 $\alpha$ )-2-(4-Chlorophenyl)octahydrocyclohept[*e*][1,3]oxazin-4(4 $\alpha$ *H*)-one (80CSC341).



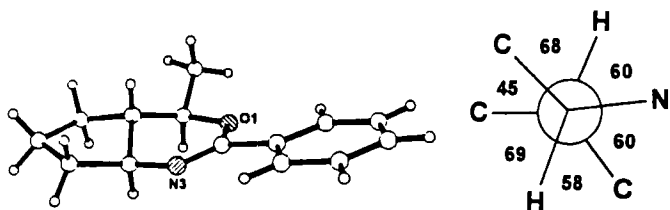
*cis*-Hexahydrospiro[cyclohept[*e*][1,3]oxazine-2(3*H*)-1'-cyclopentan]-4(4*aH*)-one [89JST(192)125]



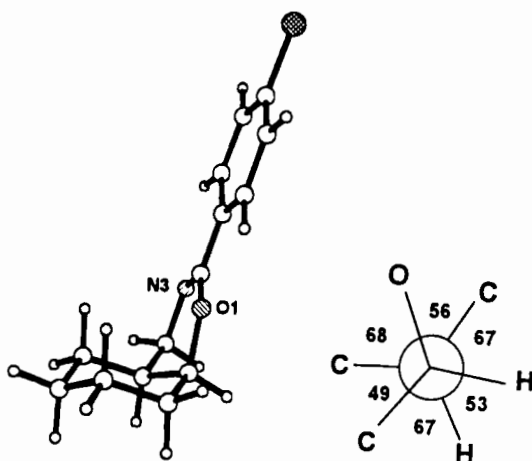
*trans*-Hexahydrospiro[cyclohept[*e*][1,3]oxazine-2(3*H*),1'-cyclopentan]-4(4*aH*)-one [89JST(192)125]



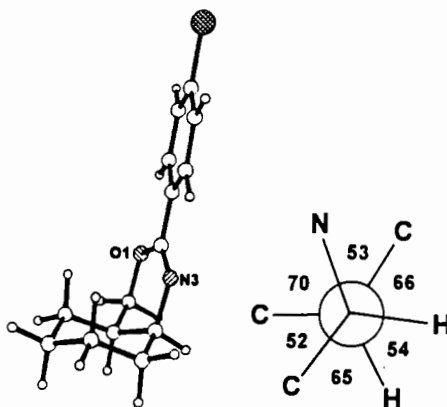
(4 $\beta$ ,4 $\alpha\alpha$ ,7 $\alpha\beta$ )-Tetrahydro-4-methyl-3-phenylcyclopent[*d*][1,3]oxazine (86JOC3248)



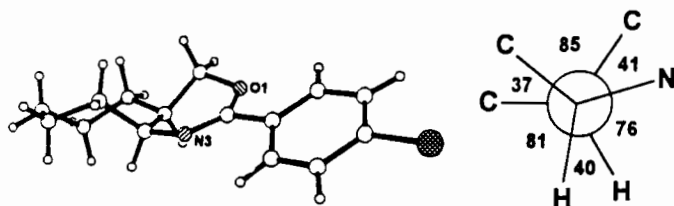
*cis*-2-(4-Chlorophenyl)-4a,5,6,7,8,8a-hexahydro-4*H*-1,3-benzoxazine (79T799)



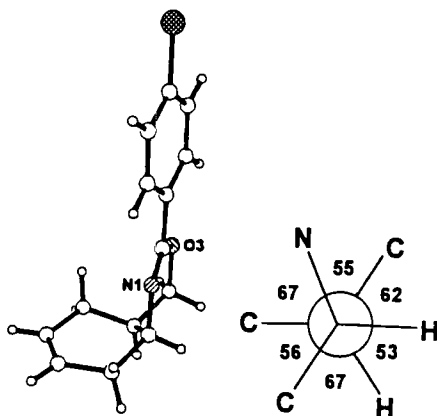
*cis*-2-(4-Chlorophenyl)-4a,5,6,7,8,8a-hexahydro-4*H*-3,1-benzoxazine (79T799)



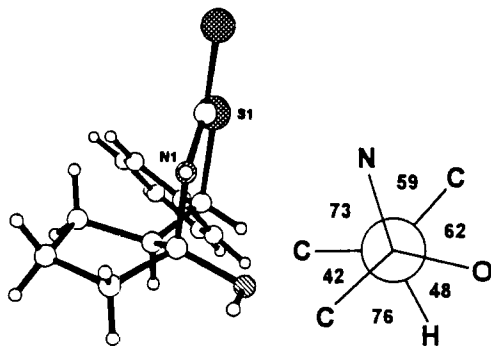
*cis*-2-(4-Chlorophenyl)-4,4a,5,6,7,8,9,9a-octahydrocyclohept-[*e*][1,3]oxazine (77CSC671)



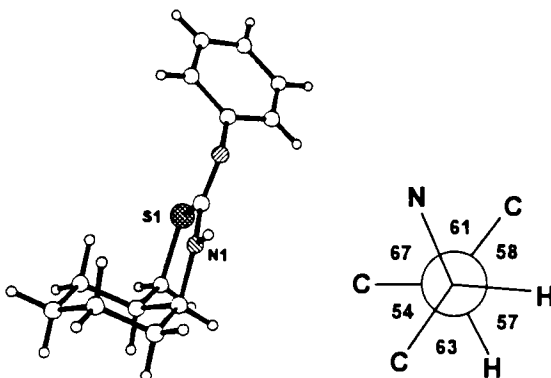
*cis*-2-(4-Chlorophenyl)-4a,5,8,8a-tetrahydro-4*H*-3,1-benzoxazine  
[86AX(C)1883]



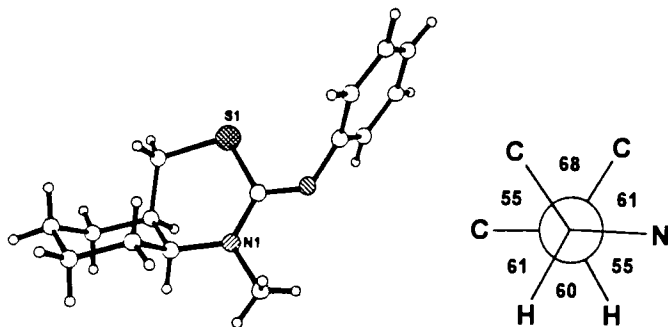
b. *Thiazine Derivatives*  
(4 $\alpha$ ,4 $\alpha\beta$ ,7 $\alpha\beta$ )-Hexahydro-7 $\alpha$ -hydroxy-4-phenylcyclopenta[*d*][1,3]thiazine-  
2(1*H*)-thione [87AX(C)324]



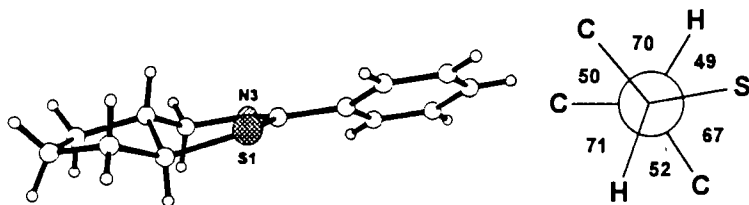
*cis*-4a,5,6,7,8,8a-Hexahydro-*N*-phenyl-4*H*-3,1-benzothiazine-2-amine  
[87JST(161)125]



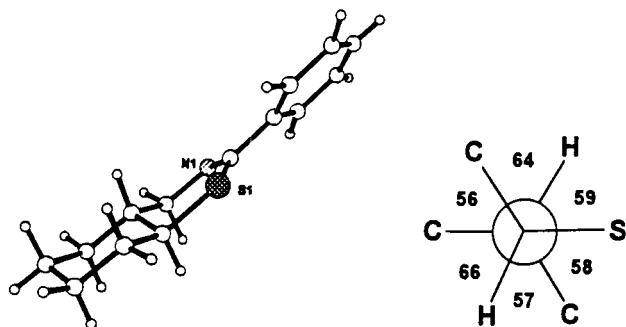
*cis*-*N*-(Octahydro-1-methyl-2*H*-3,1-benzothiazin-2-ylidene)benzeneamine  
[87JST(161)125]



*trans*-4,4a,5,6,7,7a-Hexahydro-2-phenylcyclopenta[*e*][1,3]thiazine  
[86JST(140)327]

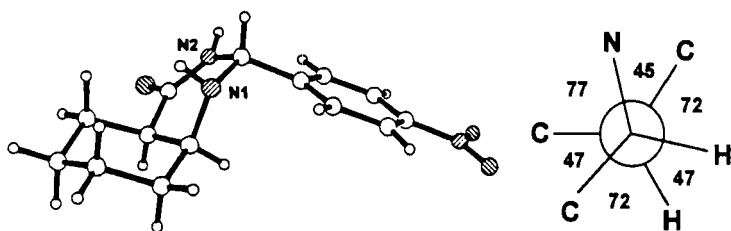


*trans*-4a,5,6,7,8,8a-Hexahydro-2-phenyl-4*H*-1,3-benzothiazine  
[86JST(140)327]

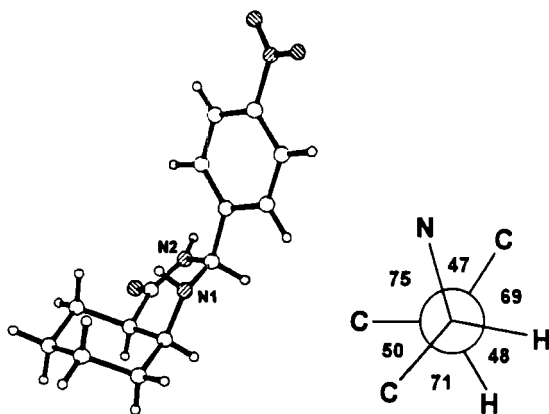


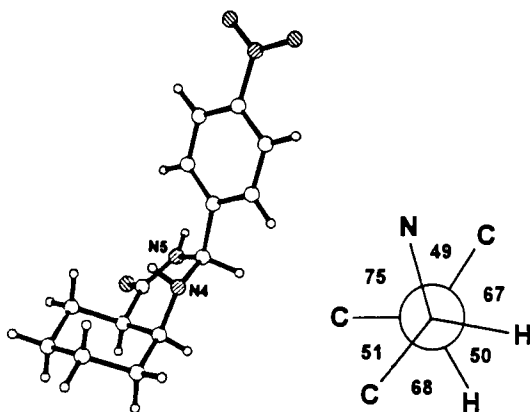
*c. Pyrimidine Derivatives*

(2 $\alpha$ ,4 $\alpha\beta$ ,8 $\alpha\beta$ )-Octahydro-2-(4-nitrophenyl)-4(1*H*)-quinazolinone  
(87T4731)

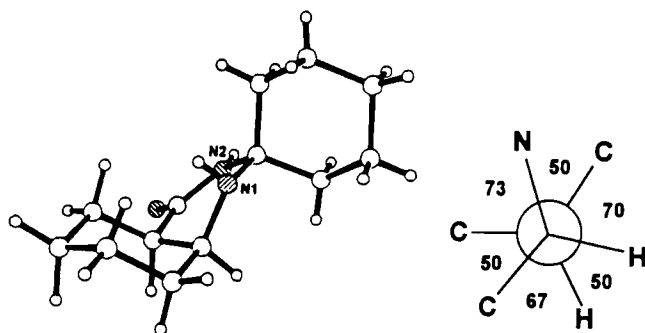


(2 $\alpha$ ,4 $\alpha\beta$ ,8 $\alpha\alpha$ )-Octahydro-2-(4-nitrophenyl)-4(1*H*)-quinazolinone  
(87T4731)

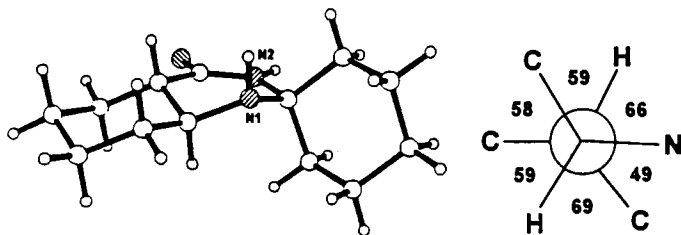




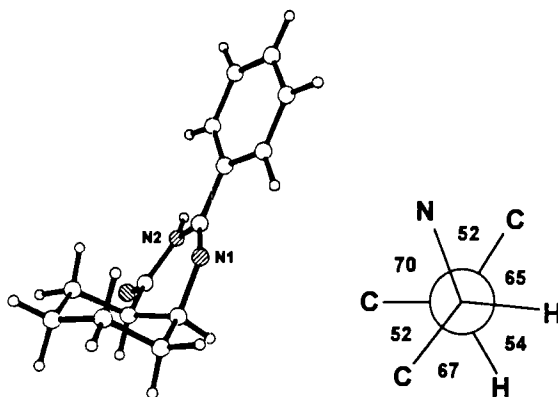
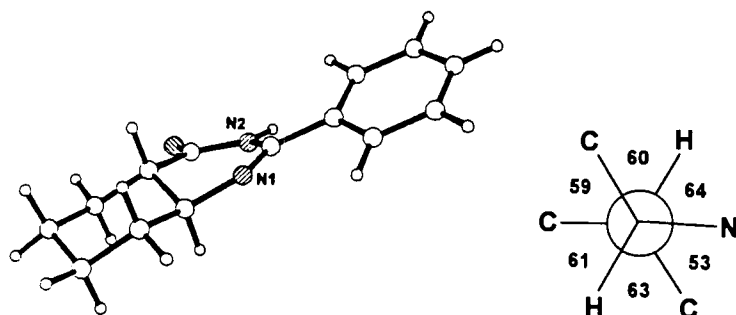
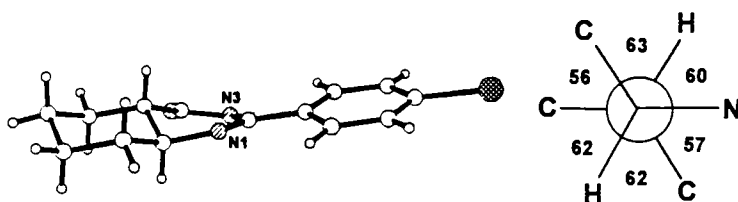
*cis*-Hexahydrospiro[cyclohexane-1,2'(1'*H*)-quinazolin]-4'(3'*H*)-one  
[91AX(C)2632]



*trans*-Hexahydrospiro[cyclohexane-1,2'(1'*H*)-quinazolin]-4'(3'*H*)-one  
[91AX(C)2632]





*cis*-4a,5,6,7,8,8a-Hexahydro-2-phenyl-4(3*H*)-quinazolinone (80CSC343)*trans*-4a,5,6,7,8,8a-Hexahydro-2-phenyl-4(3*H*)-quinazolinone (80CSC347)*trans*-4a,5,6,7,8,8a-Hexahydro-2-(4-bromophenyl)-4(3*H*)-quinazolinone (79CSC671)

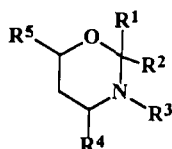
## IV. Chemical Properties

### A. GENERAL CHARACTERIZATION

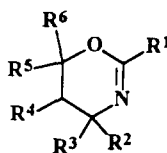
#### 1. Mass Spectrometry

Electron ionization (EI) mass spectrometry has been successfully applied to establish effects caused by stereochemistry, degree of saturation, and substitution on the characteristic fragmentations of cycloalkane-fused 1,3-oxazines, 1,3-thiazines, and pyrimidines and some of their precursor amino alcohols.

EI mass spectral fragmentations of tetrahydro-1,3-oxazine and 12 *N*- or *C*-alkyl derivatives **359** indicate that the nitrogen atom (i.e.,  $\alpha$ -cleavage) has a predominant role in the fragmentations observed (90RCM77). Retro Diels–Alder (RDA) cleavage with the formation of rearrangement ions dominated the EI spectra of several substituted 5,6-dihydro-4*H*-1,3-oxazines **360** (88KGS1539).



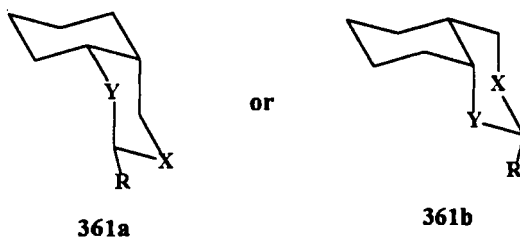
**359**



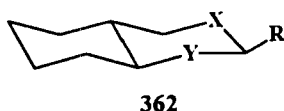
**360**

The papers in which EI mass spectrometry was applied to study ring-chain tautomerism in 2-aryl- (90T3683) and 2-heteroaryl-substituted oxazolindines [93MI1; 94H(37)1093], 2-aryl-substituted perhydro-1,3-oxazines, and 1,2-dihydro-4*H*-3,1-benzoxazines (91OMS438), as well as an EI/CI report dealing with the tautomerism of some amino diol and amino alcohol derivatives (95RCM916) in the gas phase, may also be found useful. An article (94OMS126) discussing EI and CI mass spectrometry in the stereochemical differentiation of some 1,3-amino alcohols can be related to the behavior of their cyclic derivatives.

a. *2H*-1,3- and -3,1-Benzoxazines. The EI mass spectra of *cis*-fused 3-methyl- and *cis*- and *trans*-fused 2,3-dimethyloctahydro-2*H*-1,3- and -3,1-benzoxazines (**361** and **362**) clearly differentiated these two sets of constitutional isomers (88RCM229). Even the mass spectra of the *cis*- and *trans*-fused forms can be distinguished on the basis of some intensity differences caused by stereochemical effects. However, the epimeric *cis*-fused 2,3-dimethyloctahydro-2*H*-3,1-benzoxazines gave indistinguishable spectra.



R	X	Y	R	X	Y
H	O	NMe ( <i>ax</i> )	H	O	NMe ( <i>eq</i> )
Me	O	NMe ( <i>ax</i> )	Me	O	NMe ( <i>eq</i> )
Ar	NH	O	H	NMe ( <i>eq</i> )	O
Ar	O	NH	Me	NMe ( <i>eq</i> )	O
			Ar	NH	O
			Ar	O	NH

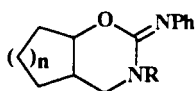


R	X	Y
Me	NMe ( <i>ax</i> )	O
Me	O	NMe ( <i>ax</i> )
Ar	NH	O
Ar	O	NH

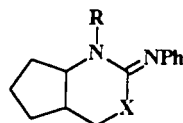
The EI mass spectrometry of 27 2-(X-substituted-aryl)-substituted octahydro-1,3-2*H*- and -3,1-benzoxazines (**361** and **362**) showed that the structural isomers clearly exhibit different spectra, although stereoisomeric differentiation was possible only for the 1,3 derivatives (93RCM465). The fragment ion peaks proved that these compounds exist in ring-chain equilibria in the gas phase as well, and the electron-withdrawing ability of the substituent X on the 2-phenyl group increases the abundance of the fragments originating from the ring form.

Two reports deal with the EI mass spectra of some related, stereoisomeric and partly saturated 1,3- and 3,1-benzoxazino-1,3-benzoxazines (95RCM1035) and of some substituted stereoisomeric 1,6,7,11b-tetrahydro-2*H*,4*H*[1,3]oxazino[4,3-*a*]isoquinolines and 1,6,7,11b-tetrahydro-2*H*[1,3]oxazino[4,3-*a*]isoquinolin-4-ones (95RCM998, 95RCM1035).

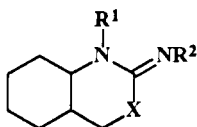
b. *2-N-Phenyl- and -Methylimino Derivatives.* The *cis*- and *trans*-fused 2-*N*-phenyliminooctahydrocyclopent[*d*][1,3]oxazines **363** and the related thiazines **364** undergo rearrangement reactions between the hydrogen atom at the *ortho* position of the phenyl ring and one of the hetero atoms in the oxazine/thiazine ring (95RCM615). All of the compounds exhibited an abundant  $[M-H]^+$  ion peak, which decreased with increasing size of the substituent (H, Me,  $CH_2Ph$ ) on the ring nitrogen. This indicates an intramolecular cyclization prior to further fragmentation. The *N*-methyl substitution changed the character of the intramolecular cyclization and also permitted the differentiation of the stereoisomers on the basis of their fragmentations. The behavior of 2-*N*-phenyliminooctahydro-2*H*-3,1-benzoxazines and related thiazines **365** (90RCM279) resembled that of the cyclopentane-fused compounds, except that the fragmentation of the *cis*- and *trans*-fused *N*-methyl-substituted compounds did not reveal stereospecificity.

**363**

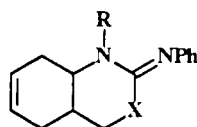
*cis, trans*; R = H, Me;  
n = 1, 2

**364**

*cis, trans*; X = O, S;  
R = H, Me,  $PhCH_2$

**365**

*cis, trans*; X = O, S;  
R = Me, Ph;  $R^1$  = H, Me,  $PhCH_2$

**366**

*cis, trans*; X = O, S;  
R = H, Me,  $PhCH_2$

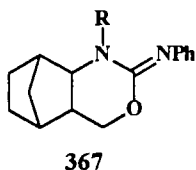
In the EI spectra of unsubstituted 2-*N*-methyliminooctahydro-2*H*-3,1-benzoxazines and related thiazines **365** (91RCM230), simple  $\alpha$ -cleavages predominated, often accompanied by a hydrogen transfer to the neutral fragment lost, with respect to the ring nitrogen atom. Substitution (Me,  $CH_2Ph$ ) on the ring nitrogen caused more extensive hydrogen migrations to the heterocyclic moiety of the molecule. Again, compounds with methyl substitution on the ring nitrogen display noteworthy stereospecificity, allowing stereoisomeric differentiation.

The EI mass spectra (89JHC1453) of four monocyclic 2-*N*-phenylimino-perhydro-1,3-oxazines (**369**) and four 2-*N*-phenyliminooctahydrocyclo-

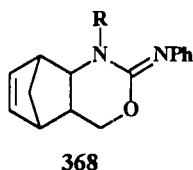
pent[*e*][1,3]oxazine and -2*H*-1,3-benzoxazines (**363**) demonstrated extensive rearrangement reactions, again best described in terms of intramolecular cyclizations. When *R* = H, *N*-cyclization is almost exclusive, whereas when *R* > H, steric reasons render *O*-cyclization more feasible. Part of the fragmentation of the *R* = H compounds seems to occur via the amino form. The methane CI spectra of *cis*- and *trans*-fused **363** (*R*, *R*<sup>1</sup>, *R*<sup>2</sup> = H) proved that at least some imino structure is present in the gas phase.

For 2-*N*-phenylimino-1,4,4a,5,8,8a-decahydro-2*H*-3,1-benzoxazines and related thiazines **366** (91MI2), the RDA reaction is the most important primary fragmentation. The electronic effects of the substituent on the ring nitrogen decrease its predominance and the *N*-benzyl substituent already dominates the fragmentations. All the compounds studied formed the ion [M-H]<sup>+</sup> through the intramolecular cyclization mentioned earlier. The abundance of these ions depends both on the *N*-substituent and on the stereochemistry of the ring fusion. Stereochemistry similarly plays an important role in other fragmentations, making differentiation of the *cis*- and *trans*-fused isomers easy.

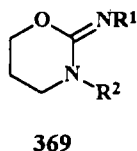
The EI fragmentation patterns of 2-*N*-phenylimino-octahydro- **367** and -1,4,4a,5,8,8a-decahydro-5,8-methano-2*H*-3,1-benzoxazines **368** (94JHC893) indicate that the *diexo/endo*-isomeric unsaturated compounds **368** cannot, whereas the saturated **367** can, be differentiated on the basis of their EI mass spectra. The former decomposed mainly in two consecutive RDA reactions, whereas the latter fragmented through several pathways, including the formation of ions [M-H]<sup>+</sup> through intramolecular cyclization.



*diendo, diexo*  
*R* = H, Me



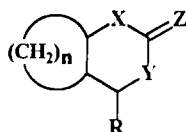
*diendo, diexo*  
*R* = H, Me



*R*<sup>1</sup> = Ph, *o*-MeC<sub>6</sub>H<sub>4</sub>, *o,o'*-diMeC<sub>6</sub>H<sub>3</sub>  
*R*<sup>2</sup> = H, Me

*c. 2-Oxo and 2-Thioxo Derivatives.* The EI fragmentation patterns of *cis/trans*-fused 2-oxo- and 2-thioxooctahydro-2*H*-1,3-benzoxazines **370** (90ACSA165) and -cyclopent[*e*][1,3]oxazines **370** (91JHC253) clearly differ from those of the corresponding 3,1-benzoxazines **370** (90ACSA165), making it easy to distinguish these structural isomers. Identification of the *cis*- and *trans*-fused isomers is made possible only by certain fragmentations that favor one or the other stereoisomer. Changes in the size of the fused

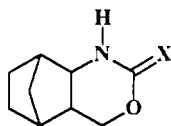
cycloalkane ring have little or no effect on the fragmentations (91JHC253). In contrast with the thioxo compounds, oxo compounds are very unstable under EI (89KGS1668; 90ACSA165; 91JHC253). No gas-phase enolization or thienolization could be found, except for the compounds with 4 $\beta$ -phenyl substitution (91JHC253).



370

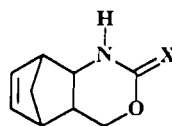
n	R	X	Y	Z	ring-fusion
3	Ph	O	NH	O	<i>cis</i>
3	Ph	O	NH	S	<i>cis</i>
3	Ph	O	NH	O	<i>cis</i>
3	Ph	O	NH	S	<i>cis</i>
4	H	O	NH	S	<i>cis/trans</i>
4	H	O	NMe	S	<i>cis/trans</i>
4	H	NH	O	S	<i>cis/trans</i>
4	H	O	NH	O	<i>cis/trans</i>
4	H	NMe	O	O	<i>cis</i>
0	H	O	NH	S	—

The EI mass spectra of *diexo*- and *diendo*-fused 2-oxo- and 2-thioxooctahydro- (**371**) and -1,4,4a,5,8,8a-decahydro-5,8-methano-2*H*-3,1-benzoxazines (**372**) (90OMS615) did not permit isomeric differentiation. The fragmentations of the former compounds are dominated by complicated ring cleavages, including several rearrangements, whereas those of the latter exhibit an RDA + H process as the most favored decomposition pathway. Under ammonia CI conditions, stereochemical effects are more perceptible, but isomeric differentiation is still difficult.



371

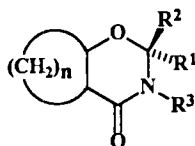
*diendo, diexo*; X = O, S



372

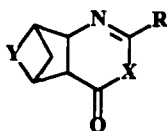
*diendo, diexo*; X = O, S

d. *4-OxoDerivatives.* An article on the EI mass spectra of *cis*- and *trans*-fused octahydro-2*H*-1,3-benzoxazin-4-ones **373** (85JHC523) indicates that the roles of C-2 and N-3 substituents are characteristic, whereas the size of the cycloalkane ring seems to be unimportant. Again, some fragmentation processes including oxazinone ring cleavage display significant stereoselectivity.

**373**

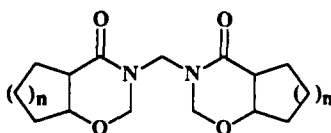
n	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Fusion
3	<i>o</i> -ClC <sub>6</sub> H <sub>4</sub>	H	H	<i>cis</i>
3	<i>m</i> -ClC <sub>6</sub> H <sub>4</sub>	H	H	<i>cis</i>
3	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	H	H	<i>cis</i>
4	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	H	H	<i>cis/trans</i>
5	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	H	H	<i>cis/trans</i>
3	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	H	Me	<i>cis</i>
4	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	H	Me	<i>cis</i>
5	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	H	Me	<i>cis</i>
4	H	H	Me	<i>cis/trans</i>
4	Me	Me	H	<i>cis/trans</i>
3	-(CH <sub>2</sub> ) <sub>5</sub> -		H	<i>cis</i>
4	-(CH <sub>2</sub> ) <sub>5</sub> -		H	<i>cis/trans</i>
5	-(CH <sub>2</sub> ) <sub>5</sub> -		H	<i>cis/trans</i>
4	-(CH <sub>2</sub> ) <sub>6</sub> -		H	<i>cis</i>

In another paper, the main EI fragmentation processes of three pairs of *diexo*- and *diendo*-fused 1,4,4a,5,8,8a-decahydro-5,8-methano-2*H*-3,1-benzoxazin-4-ones **374** (91IJM225; 91MI2) were established by means of mass spectrometry and MNDO calculations. The EI mass spectrometric fragmentations of the bis-oxazinones **375** have also been reported [79ACH(101)61].



*diexo*, *diendo*; R = Ph, *p*-MeC<sub>6</sub>H<sub>4</sub>, *p*-ClC<sub>6</sub>H<sub>4</sub>

	X	Y
<b>374</b>	O	CH <sub>2</sub> CH <sub>2</sub>
<b>376</b>	NH	CH=CH, CH <sub>2</sub> CH <sub>2</sub>



**375**

*cis*: n = 1-3; *trans*: n = 2, 3

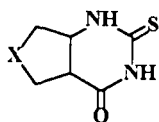
e. *Pyrimidin-4-ones*. The main EI-induced fragmentations of three pairs of *diexo*- and *diendo*-fused octahydro- and three *diendo* 1,4,4a,5,8,8a-decahydro-5,8-methano-2*H*-3,1-quinazolin-4-ones **376** were likewise established by means of mass spectrometry and MNDO calculations (91MI2). The relative abundances of various fragment ions and also those of the molecular ions differ for the *diexo* and *diendo* isomers of the former compounds.

*cis*-Fused 2-thioxooctahydro-1*H*-cyclopentapyrimidin-4-one, *cis/trans*-fused 2-thioxodecahydroquinazolines, and *trans*-fused 2-thioxo-1,2,3,4,4a,5,8,8a-octahydroquinazoline **377** are easy to distinguish from each other on the basis of their EI mass spectra (91OMS493).

An EI report deals with the tautomerism of unsubstituted and the differentiation of substituted pyrimidin-4(3*H*)- and -4(1*H*)-ones (90OMS115). Another publication on 2-alkyl (Et, Pr) or 2-arylmethyl-substituted derivatives shows that the substituent decisively influences their fragmentation and that, especially in the case of 2-arylmethyl substituents, an intramolecular cyclization in the formation of the ion [M-H]<sup>+</sup> again becomes very important (94MI4). Two reports deal with the EI spectra of partly saturated tricyclic double-fused pyrimidinone (one *N* at bridgehead) derivatives (93OMS18; 94RCM535).

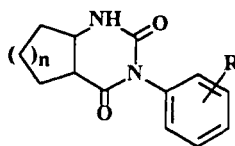
The EI fragmentation of 2-thioxo-2,3-dihydroquinazolidin-4(1*H*)-one has also been studied (93RCM374).





377

X	ring-fusion
CH <sub>2</sub>	<i>cis</i>
CH <sub>2</sub> CH <sub>2</sub>	<i>cis/trans</i>
CH=CH	<i>trans</i>



378

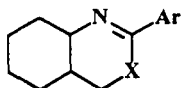
*cis, trans*; R = H, *m*-Cl, *p*-Cl, *o*-Cl;  
n = 1, 2

f. *Pyrimidine-2,4-diones*. The fragmentation patterns of *cis*- and/or *trans*-fused octahydro-1*H*-cyclopentapyrimidine-2,4-diones and decahydroquinazoline-2,4-diones **378** (90OMS277) are clearly different, and the mass spectra of *cis*- and *trans*-fused isomers are easy to distinguish from each other. All compounds, however, fragment into phenyl isocyanates and anilines.

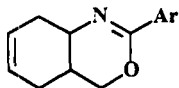
The constitutionally isomeric 3-substituted (1*H*,3*H*)-quinazoline-2,4-diones and 2-phenylimino-4*H*-3,1-benzoxazin-4-ones are easy to distinguish via their EI mass spectra (93RCM374). For quinazolinediones, the most striking feature is the loss of CO<sub>2</sub>, proving that a rearrangement due to anilino migration must occur.

## 2. Polarography

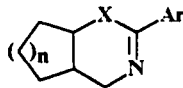
The polarography of a number of alicycle-fused oxazine, thiazine, and pyrimidine derivatives of the types **379–384** (X = O, S; n = 1, 2, 3) containing endocyclic or exocyclic C=N bonds has been studied by means of



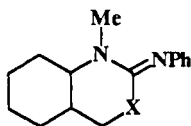
379



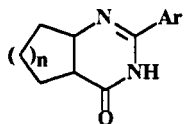
380



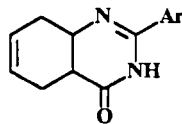
381



382



383



384

dc and ac polarography at the dropping mercury electrode (81PHA863; 83PHA373, 83PHA841; 86PHA432; 87PHA270, 87PHA505, 87PHA601, 87PHA721; 90PHA568). In many cases, clear-cut differences were found in the half-wave potentials of the *cis*- and *trans*-fused isomers. In general, the *trans* isomers were reduced more easily than the corresponding *cis* isomers, because of their flatter, more closely planar structure. The effects of the substituents and the ring size were also investigated. The reduction products were often isolated. These investigations were reviewed some years ago (88MI2, 88MI3).

### 3. Tautomerism of 2-Imino-Substituted 1,3-Oxazines and 1,3-Thiazines

Although the amino-imino tautomerism of 2-imino-substituted tetrahydro-1,3-oxazines and thiazines is a known process [78AHC(23)1], which in some cases has been measured accurately [e.g., (91JOC3194)], for the investigated cycloalkane-fused derivatives only the preference of the imino tautomer has been detected (see Sections II,A,2,c and II,B,1) [85T5981; 87JCS(P2)599, 87M503]. X-ray measurements demonstrate the imino form for each structure (see Section III,B,6) [(87JST(161)125].

### 4. Ring-Chain Tautomerism of Tetrahydro-1,3-oxazines

The ring-chain tautomerism of tetrahydro-1,3-oxazines, which involves the reversible addition of a hydroxy group to a C = N bond, is a well-established process and was reviewed recently [94ACH(131)697; 95AHC(64)251; 96AHC(66)1]. In this context, only the most important characteristics of the ring-chain tautomerism of the alicycle-fused 1,3-oxazines is briefly discussed.

Since the tautomerism of a number of 2-aryl-substituted alicycle-fused systems has been studied, several general rules can be given. The tautomerism of a "d"-fused general structure, for instance, can be shown by the equilibria of two epimeric ring forms ( $R^1$ ,  $R^2$ ), and *E* and *Z* open-chain forms (**385**–**388**). In most of the equilibria, one of the epimeric ring forms greatly predominates (87JOC3821). Of the open-chain isomers, generally only the *E* form is present in the equilibria, but in some special cases the *Z* form has also been detected (90MI2; 91T4031; 93JOC1967).

The tautomerism of the 2-aryl-substituted tetrahydro-1,3-oxazines with the general structures **390**, **391**, **393**, **394**, and **396**–**406** has been studied in detail. Only the structures of the ring forms are shown. In all series, the ring-chain tautomeric equilibria measured in  $\text{CDCl}_3$  at room temperature can be described by the equation

$$\log K_X = \rho \sigma^+ + \log K_{X=H} \quad (1)$$

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where  $K_X = [\text{ring(s)}]/[\text{chain(s)}]$  and  $\sigma^+$  is the Hammett–Brown substituent constant.

The linear regression analysis data are listed in Table VIII. For ease of comparison, the data on the parent 2-aryltetrahydro-1,3-oxazine **389** and the corresponding 1,3- and 3,1-benzoxazine isomers **392** and **397** are also given. The data in Table VIII show that  $\rho$  is practically the same for all the 1,3-oxazine ring systems investigated, whereas the intercept values are characteristic of the substituents.

For characterization of the steric and electronic contributions of the substituents, the constant  $c$  was introduced and defined as the intercept difference for the basic tetrahydrooxazine system **389** and the compound in question. A positive  $c$  value indicates stabilization; a negative  $c$  value means a destabilizing effect of the substituents (Table VIII).

The tautomerism of the preceding heterocycles can also be detected in the gas phase by mass spectrometry (91OMS438; 93MI1), but it cannot be described by the equation just given, as was the case with oxazolidines (90T3683).

The solid-state NMR spectra of perhydrobenzoxazines of types **390**, **391**, **393**, and **394** show that the chain form is preferred in those cases where less than 80% of the ring tautomer is present in  $\text{CDCl}_3$  solution (92T4979; 95MRC600).

The general Eq. (1) and the actual slope and intercept values were successfully used to determine the Hammett–Brown substituent constants of six- and five-membered heterocycles [91ACSA273; 94H(37)1093].

With the aid of ring–chain tautomerism, numerous reactions of the tetrahydrooxazines, such as ring opening with nucleophiles (Section IV,B,1), C-2 epimerization (Section II,A,1), and transimination [72ACH(73)81; 87ACSA(B)147] can be rationalized.

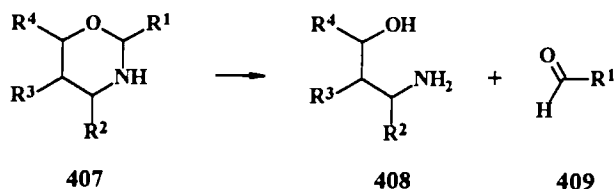
## B. CHEMICAL TRANSFORMATIONS

### 1. Ring-Opening Reactions with Nucleophiles

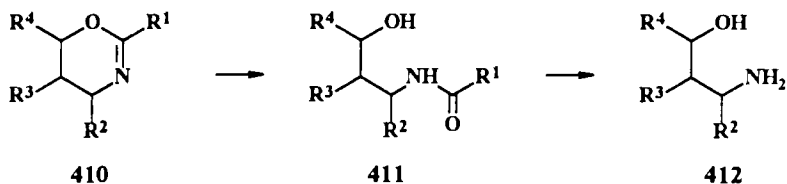
a. *Hydrolysis, Alcoholysis, and Ammonolysis.* Tetrahydro-1,3-oxazines and different dihydrooxazines are sensitive substances. On nucleophilic attack, ring opening is the characteristic reaction.

Acid hydrolysis of tetrahydrooxazines **407** is well known and widely used for the synthesis of amino alcohols **408** or for the enantioselective synthesis of aldehydes **409**, which can be transformed to carboxylic acids by mild oxidation [78AHC(23)1; 87JCS(P1)515, 87T4979; 90JOC2114].

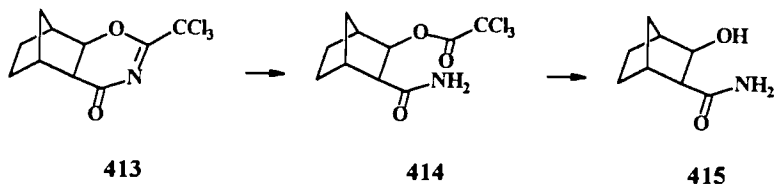
On acid or alkaline hydrolysis, the dihydrooxazines **410** give *N*-acyl derivatives **411** [74CCC1447; 82ZOR181; 85ACH(118)139; 93T3907]. Under



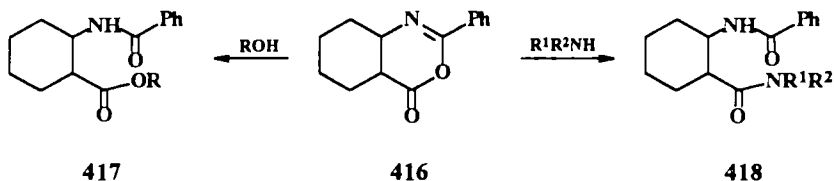
more forcing acidic conditions, the *N*-acyl group is also hydrolyzed, resulting in the amino alcohols **412** (76LA2105; 79T799; 82ZOR181; 84CB3205).



Some saturated 1,3-benzoxazinones, such as **413**, are very sensitive to humidity (69JOC633). Under aqueous conditions, formation of the trichloroacetate **414** is a fast process. On aqueous alkaline hydrolysis, the 2-hydroxy-1-carboxamide **415** is formed (69JOC633; 73JOC414; 74JA6492; 84CB3205), whereas acid hydrolysis of **414** gives the corresponding hydroxy acid (74JA6492).



Alcoholysis of the *cis* and *trans* isomers of the dihydrooxazinone **416** was performed with ethanol, *n*-butanol, 3-phenylbutanol, and menthol, resulting in the corresponding *N*-benzoylamino esters **417** in excellent yields [77H(7)301]. The aminolysis of **416** with ammonia, aniline, benzylamine, or dibutylamine gave the carboxamides **418** in 52–99% yields [77H(7)301].

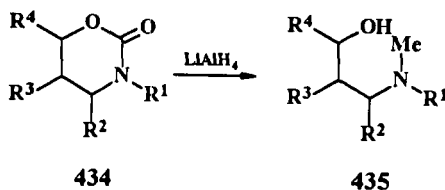


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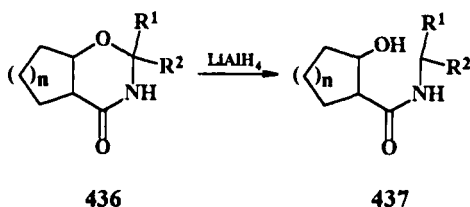
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Lithium aluminum hydride reduction of tetrahydro-1,3-oxazin-2-ones **434** results in the corresponding *N*-methyl-substituted 1,3-amino alcohols **435** (60JA4656; 87TL1623).



Lithium aluminum hydride reduction of the tetrahydro-1,3-oxazin-4-ones **436** (*cis*,  $n = 1, 2$ ; *trans*,  $n = 2$ ;  $R^1, R^2 = \text{H, alkyl, aryl}$ ) can easily be performed in tetrahydrofuran, resulting in the *N*-substituted amino alcohols **437**. In the case of monosubstituted derivatives, the reduction takes place at room temperature, while the 2,2-disubstituted derivatives have been reduced in boiling tetrahydrofuran (81S628; 83T1829).

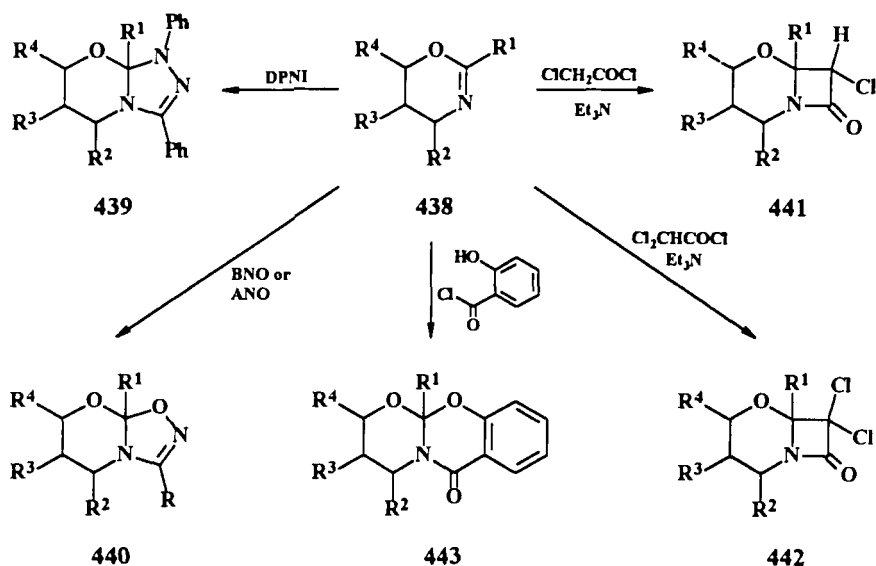


## 2. Cycloadditions

A number of different cycloaddition reactions have been carried out on the  $\text{C} = \text{N}$  double bond of dihydrooxazines with the general structure **438** (Section II,A,5). With diphenylnitrilimine (DPNI), generated *in situ* from *N*-( $\alpha$ -chlorobenzylidene)-phenylhydrazine with triethylamine, the 1,2,4-triazolo[3,4-*b*][1,3]oxazines **439** were prepared (87MRC635, 87T1931, 87T5461).

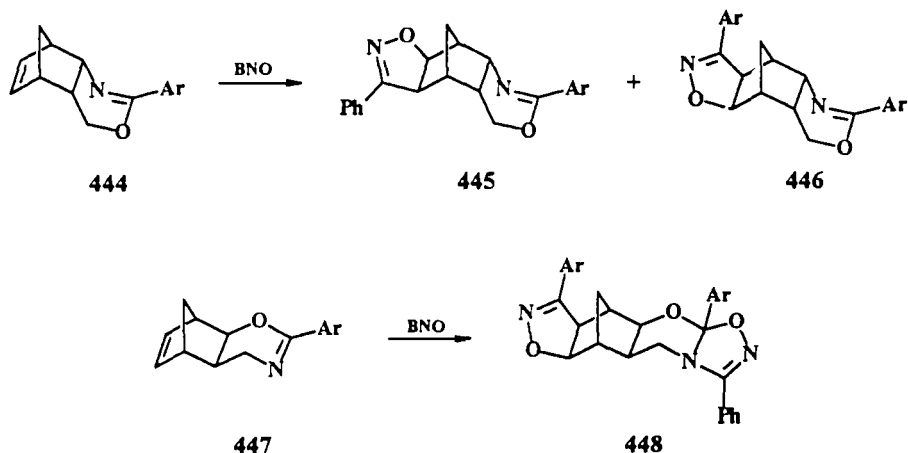
With benzonitrile oxide (BNO) or acetonitrile oxide (ANO), obtained from benzhydroxamic chloride or from nitroethane and phenyl isocyanate in the presence of triethylamine, the 1,2,4-oxadiazolo[2,3-*b*][1,3]oxazines **440** (87MRC635, 87T1931, 87T5461; 91MRC706) were obtained.

Chloroacetyl chloride or dichloroacetyl chloride and triethylamine form a ketene, which reacts with **438** in a  $[2 + 2]$  cycloaddition, resulting in azeto[2,1-*b*][1,3]oxazines **441** and **442**, respectively [85T1721; 89MRC872; 93H(36)995].



Oxazines **438** and salicyl chloride gave the 1,3-benzoxazino[2,3-*b*][1,3]oxazines **443** (91JHC753). The reactions were generally stereospecific, but in some cases diastereomers were also isolated.

An interesting observation was made in the study of BNO or ArNO addition to norbornene dipolarophiles **444** and **447**, which contain C = N and C = C bonds. With BNO or ArNO, the isoxazoline regioisomers **445** and **446** were unexpectedly obtained by addition to the olefinic double bond. In the case of the *exo* isomers **447**, addition took place to both the

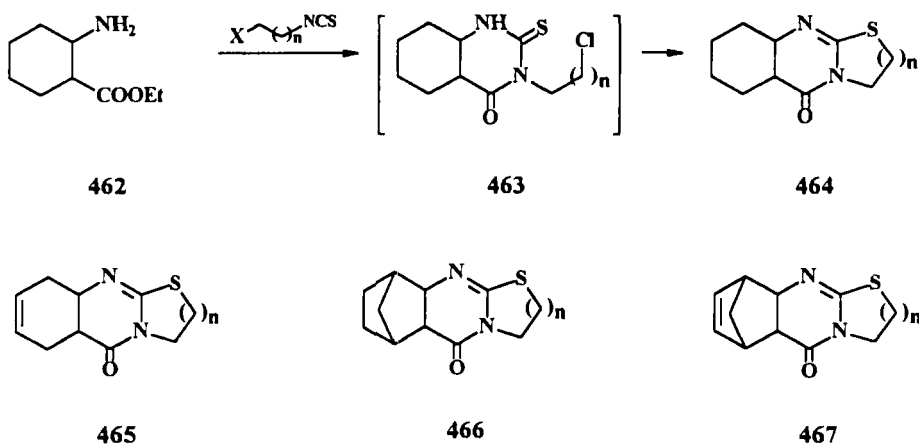


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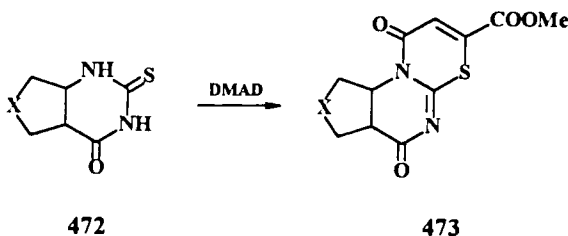
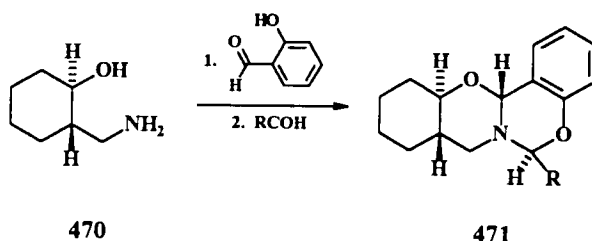
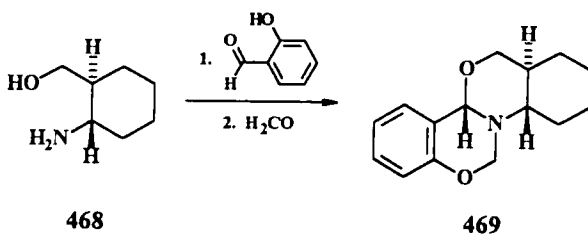
of the quinazolinone intermediate **463** (see also Section II,C,3), which yields the tricyclic end product in a fast thioalkylation process.

Cyclization of the isothiocyanates obtained from alicyclic  $\beta$ -amino esters with thiophosgene and 2-chloroethyl or 3-chloropropylamine gave the thiazolopyrimidinones **464–467** (96UP2).



*b. Cyclizations on Ring Nitrogen and on Side-Chain Functional Groups.* By treatment of *trans*-2-hydroxymethyl-1 cyclohexylamine **468** with salicylaldehyde and subsequently with formaldehyde, the [3,1]benzoxazino[1,2-*c*][1,3]benzoxazine ring system **469** was formed stereospecifically in a facile one-pot reaction (86TL2517). The structural isomeric amino alcohol **470** was reacted with salicylaldehyde, with subsequent aldehyde treatment, to give the [1,3]benzoxazino[4,3-*b*][1,3]benzoxazines **471** ( $\text{R} = \text{H}, \text{Me}, \text{Ph}$ ) (88T2993). Surprisingly, when the corresponding *cis* amino alcohols were reacted under similar conditions, no tetracyclic products were formed, but transimination took place and the salicylaldehyde was recovered.

$^1\text{H}$  NMR investigation of the reactions of 1,3-amino alcohols and salicylaldehyde in  $\text{CDCl}_3$  proved that all these compounds exist as a ring-chain tautomeric mixture with a high preference for the open forms. It was suggested that the formation of the tetracycles is favored if the product is precipitated from the aqueous-alcoholic reaction mixture, shifting the equilibrium toward the ring form (88T2993). This assumption was successfully confirmed by using 5-bromosalicylaldehyde instead of salicylaldehyde. In these reactions, the tetracyclic products, with a better ability to crystallize, were formed even in the case of the *cis* isomers (91JHC1213).



The 4-oxo-2-thioxopyrimidines **472** (*cis*,  $\text{X} = \text{CH}_2, \text{CH}_2\text{CH}_2$ ; *trans*,  $\text{CH} = \text{CH}, \text{CH}_2\text{CH}_2$ ), readily prepared from amino esters with potassium thiocyanate, gave the tricyclic 1,3-thiazinopyrimidinones **473** by addition of dimethyl acetylene dicarboxylate (DMAD) (89MRC959). In this reaction, the first step is probably a Michael addition of DMAD to the tautomeric 2-SH group, and thereafter cyclization of the ester on the ring NH occurs.

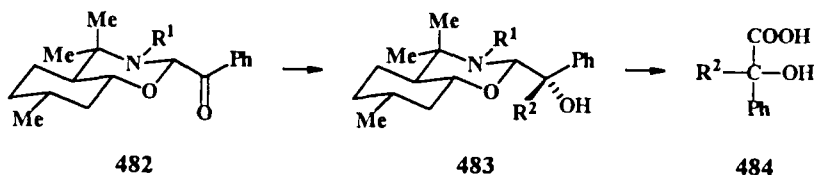
#### 4. Retro Diels–Alder Reactions

A versatile new and general method was developed for the synthesis of six-membered 1,3-heterocycles. In comparison with the general reaction conditions of retrodiene reactions, a very mild *retro* Diels–Alder (RDA) decomposition was found to occur when the norbornene-*diexo*- or -*diendo*-fused dihydrooxazinone **474** was heated at melting temperature or refluxed in different solvents (e.g., chlorobenzene). Cyclopentadiene splitted off and the 2-aryl-6*H*-1,3-oxazin-6-ones **475**, earlier unknown representatives of the simple 1,3-oxazines, were obtained (84S345, 84T2385).

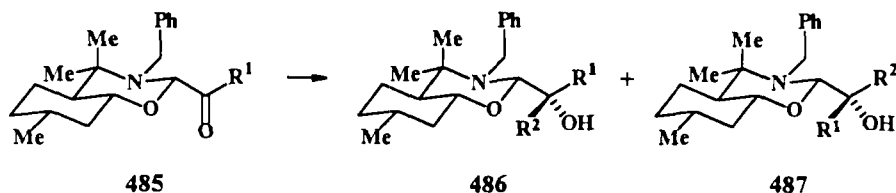
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or sodium borohydride, resulting in the alcohols **483**, **486**, and **487** in high diastereoselectivity. Oxazines **483** were readily converted to  $\alpha$ -hydroxyacids **484** by hydrolysis with dilute hydrochloric acid and subsequent oxidation in the presence of sodium chloride. The enantiomeric excess in the formation of **483** is given in Table IX, while the diastereoselectivities of the transformations **485**  $\rightarrow$  **486** + **487** are given in Table X.



As Tables IX and X show, the reactions are highly enantioselective processes. The 2-furyl-substituted derivative of **485** has also been reduced with high diastereoselectivity (94M11). Pedrosa *et al.* have used the benzoxazines **482** for the synthesis of primary amines in very good chemical yield and with high enantiomeric excess (90SL763). Consequently, the perhy-

TABLE IX  
 $\alpha$ -HYDROXY ACIDS **484** OBTAINED FROM THE 1,3-OXAZINE **483**<sup>a</sup>

$R^1$ in starting compound <b>482</b>	Reagent	$R^2$	Temperature (°C)	Yield (%)	e.e. (%)	Product configuration
CH <sub>2</sub> Ph	MeMgBr	Me	20	44	98	S
CH <sub>2</sub> Ph	MeMgBr	Me	-70		98	S
Me	MeMgBr	Me	20	26	92	S
CH <sub>2</sub> Ph	MeLi	Me	-70	47	95	S
Me	MeLi	Me	5	30	96	S
CH <sub>2</sub> Ph	EtMgBr	Et	5	77	~100	S
CH <sub>2</sub> Ph	CH $\equiv$ CMgBr	CH $\equiv$ C	20	63	97 $\pm$ 1	S
CH <sub>2</sub> Ph	$\alpha$ -NaphthylMgBr	$\alpha$ -Naphthyl	20	23	82 $\pm$ 1	R
CH <sub>2</sub> Ph	NaBH <sub>4</sub>	H	5	48	80	S

<sup>a</sup> Data from He and Eliel (87T4979) and from Eliel and He (90JOC2114).

TABLE X  
REACTIONS OF KETONES **485** TO **486** AND **487**<sup>a</sup>

Reagent	R <sup>1</sup>	R <sup>2</sup>	Temperature (°C)	Yield (%)	Diastereoselectivity		
					<b>486</b>	:	<b>487</b>
PhMgBr	Me	Ph	5	81	95.5	:	4.5
EtMgBr	Me	Et	5	97	92	:	8
<i>i</i> PrMgCl	Me	<i>i</i> Pr	5	100	96	:	4
NaBH <sub>4</sub>	Me	H	5	85–100	95.5	:	4.5
DIBAL	Me	H	–70	79	50	:	50
MeMgBr	Et	Me	5	93	96	:	4
MeMgBr	<i>i</i> Pr	Me	5	100	93.5	:	65
MeMgBr	H	Me	5	81	94.5	:	55
MeMgBr	H	Me	–70	95	91	:	9
PhMgBr	H	Ph	5	100	83.5	:	16.5
PhMgBr	H	Ph	–70	100	85	:	15

<sup>a</sup> Data from Eliel and He (90JOC2114).

drobenzoxazines **482** and **485** and their starting amino alcohols are promising synthons for further enantioselective syntheses.

## V. Applications

A number of the possible synthetic applications were illustrated in Section IV,B. Further biological and other applications of practical value are mentioned here.

Numerous dihydropyrimidin-4-one derivatives (Section II,C,5) were synthesized as saturated analogs of Methaqualone, and their analgesic, antipyretic, anti-inflammatory, and narcosis-potentiating effects were studied (77GEP2643384; 80AUP507798). In general, these compounds have low toxicity and the *cis* isomers are more active anti-inflammatory compounds than the *trans* isomers. The anti-inflammatory activity increased with decreasing size of the alicyclic ring fused to pyrimidinone. The most active compound proved to be **488** (Chinoïn 143), a 6 mg/kg oral dose of which caused a 39% inhibition of carrageenan edema in mice.

Cycloalkane-fused tetrahydro-1,3-oxazin-4-ones (Section II,A,2) related to the preceding family were also studied with the same tests (80MIP1), and the 2-(3-chlorophenyl)- and 2-(2-furyl)-substituted derivatives of **489** were found to be active compounds (82MI1; 83PHA89).

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